Archives of Neurology and Psychiatry

VOLUME 43 JUNE 1940 NUMBER 6

"BULGARIAN TREATMENT" OF PARKINSON'S DISEASE

PHARMACOLOGIC ASPECTS AND CLINICAL EFFECTS OF ALKALOIDS OF BELLADONNA ROOT

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The "Bulgarian treatment" of postencephalitic parkinsonism was originated in 1926 by the Bulgarian plant collector Ivan Raeff. In a previous publication [1] it was pointed out that the only effective component of this medication is the Bulgarian belladonna root.

PHARMACOLOGIC ASPECTS

Belladonna roots have rarely been used for therapy. Atropine, hyoscyamine, scopolamine and other alkaloids of this group are usually extracted from the leaves of Atropa belladonna, Hyoscyamus niger, Datura stramonium, Scopolia atropoides or Duboisia myoporoides. In general, these alkaloids are found in roots and leaves, but in different concentrations and in different proportions of the individual alkaloids.

Belladonna roots themselves show considerable variation in the concentration and distribution of the alkaloids, the variations depending on the age of the plant, the time of harvest, the geographic location, the climatic condition, the degree of cultivation and storage. For example, Raeff's original Bulgarian root contains 0.86 per cent of total alkaloids (Antolini-Frugoni [2]); the German root, 0.526 per cent (von Witzleben [3]); the Indian root, 1.65 per cent (von Witzleben [3]), and various Italian roots, from 0.3 to 0.71 per cent (Antolini-Frugoni [4]). Bella-

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1. Vollmer, H.: J. Mt. Sinai Hosp. **6**:93, 1939.

2. Antolini-Frugoni, A.: Resoconti del Reparto "Regina Elena," private prints of the royal institute ospedale al Policlinico Umberto I, Rome, June 1936.

3. von Witzleben, H. D.: Klin. Wchnschr. **17**:329 and 369, 1938; Deutsche med. Wchnschr. **64**:162, 671 and 1174, 1938.

4. Antolini-Frugoni, A.: Resoconti del Reparto "Regina Elena," private prints of the royal institute ospedale al Policlinico Umberto I, Rome, January 1937.

donna root U. S. P. contains not less than 0.45 per cent of alkaloids. The foregoing figures refer to analyses of individual samples from different countries and cannot be used as averages. Bulgarian as well as American roots may be rich or poor in active constituents. The total alkaloid concentration of the root does not determine its therapeutic efficacy. Rather, the proportion of the various alkaloids is the decisive factor.

The total alkaloids of belladonna root and of its extracts are determined by a titration method, which varies in the pharmacopeias of different countries. Slight discrepancies in the literature may be ascribed to differences in method. Antolini-Frugoni [2] modified the method of the official Italian pharmacopeia, which he found unsatisfactory. His modification has been accepted by many European investigators of the "Bulgarian treatment."

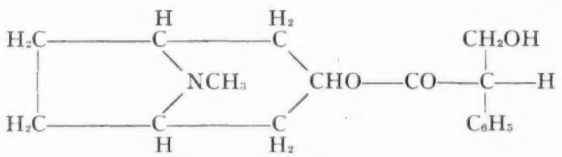
The method given in the Pharmacopeia of the United States is simpler and more reliable than the Antolini-Frugoni method, which involves numerous sources of error. The method of the United States Pharmacopeia has been used exclusively for the standardization of the extracts employed in this study.

Commercial belladonna roots are not infrequently of inferior quality due to the presence of large quantities of stem bases or to adulteration with other roots. The supposed superiority of Bulgarian roots may be ascribed partly to the care with which Raeff's roots have been collected, chosen and stored. Bulgarian roots from other sources have been found much less satisfactory in their effect on postencephalitic parkinsonism; very good results have been reported in the literature with extracts from Italian, German, Belgian and English belladonna roots.

The active properties of belladonna root can be extracted with water and alcohol. The following alkaloids are found: atropine, hyoscyamine, scopolamine, atropamine and belladonnine. Atropine is a basic ester which can be split by alkali and acid into the basic alcohol tropine and the aromatic tropic acid, according to the formula: $C_{17}H_{23}NO_3 + H_2O = C_8H_{15}NO + COOH\ C_8H_5OH$

Atropine — Tropine — Tropic acid

Willstätter [5] established the constitution of the atropine molecule as follows:



As a result of the asymmetric carbon atom of tropic acid, there exist three optically different isomers. Atropine is optically inert and is regarded as a mixture of levorotatory and dextrorotatory hyoscyamine. Dextrorotatory hyoscyamine does not occur in nature. Levorotatory hyoscyamine is the main

5. Willstätter, cited by Meyer and Gottlieb.[11]

alkaloid ingredient of belladonna root. Cushny [6] has shown that levorotatory hyoscyamine has a relatively greater paralyzing effect on nerve endings and a relatively slighter stimulating action on the central nervous system than the isomeric atropine. Hyoscyamine causes less rise in blood pressure, less increase in the respiratory rate and less delirium or hallucinations.

Scopolamine is a levorotatory alkaloid, with the formula $C_{17}H_{21}NO_4$, which occurs in small amounts in belladonna root. Its pharmacologic action is characterized by its paralyzing effect on the central nervous system. It depresses the motor centers, and its danger lies in its paralyzing action on the respiratory and circulatory centers.

Belladonnine and atropamine are anhydroatropines, of the formula $C_{17}H_{21}NO_2$, which are found at times, and only in slight concentrations, in belladonna root.

Atropamine is identical with apoatropine, which has been isolated by Hesse [7] and Merck.[8] The recent studies of Kreitmair and Wolfes [9] and of Duensing [10] have aroused interest in apoatropine. On the basis of experiments with animals, Meyer and Gottlieb [11] asserted that apoatropine is extremely toxic, with selective stimulating action on the central nervous system. Duensing, however, who first administered this alkaloid to human beings, found a high tolerance to the drug and a beneficial effect on postencephalitic parkinsonism. Since the concentration of apoatropine in extracts of belladonna root is low, the efficacy of these extracts in parkinsonism cannot be ascribed to this alkaloid.

Belladonnine was isolated by Küssner [12] and was found to be a dimer of apoatropine.

The alkaloids of belladonna root have been extracted by different methods. Panegrossi,[13] who introduced the Bulgarian treatment into scientific medicine, used the original wine decoction, as directed by Raeff, for several years.

Thirty grams of belladonna roots is boiled continuously in 600 cc. of white wine for ten minutes. This decoction is cooled, filtered and kept in tightly closed bottles. The alkaloid content is, on the average, 0.02 per cent, but varies considerably. In addition, the decoction is unstable and impractical because it has to be administered in large quantities. Therefore its use has generally been abandoned.

Antolini-Frugoni [14] devised the following improved method of cold extraction:

Belladonna root . . . . 6,000 Gm. Distilled water . . . . 25,500 cc. 95 per cent alcohol . . . . 4,500 cc. Tartaric acid . . . . 300 Gm.

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6. Cushny, A. R.: J. Physiol. **30**:176, 1903.
7. Hesse: Mercks Jahresber., 1892, pp. 3-12; 1893, pp. 3-9.
8. Merck, E.: Ann. d. Chem. **277**:290, 1893.
9. Kreitmair, H., and Wolfes, O.: Klin. Wchnschr. **17**:1547, 1938.
10. Duensing, F.: Klin. Wchnschr. **17**:1550, 1938.
11. Meyer, H. H., and Gottlieb, R.: Experimentelle Pharmakologie als Grundlage der Arzneibehandlung, Berlin, Urban & Schwarzenberg, 1933.
12. Küssner, W.: Ber. d. deutsch. pharm. Gesellsch., vol. 276, p. 617.
13. Panegrossi, G.: Policlinico (sez. prat.) **42**:56, 506 and 1487, 1935; Riv. osp. **27**:3, 1937; Deutsche med. Wchnschr. **64**:669, 1938.
14. Antolini-Frugoni, A.: Resoconti del Reparto "Regina Elena," private prints of the royal institute ospedale al Policlinico Umberto I, Rome, December 1936; July 1937.

The mixture is macerated for thirty hours, and subsequently percolated. This extract contains from 0.09 to 0.1 per cent of alkaloids. A second maceration of belladonna roots, for twenty-four hours, is made with a solvent consisting of 12,750 cc. of distilled water and 2,250 cc. of 95 per cent alcohol. The second extraction usually yields from 0.05 to 0.07 per cent of alkaloids.

For economic reasons, Antolini-Frugoni[14] eliminated the use of alcohol and replaced it with an aqueous solvent containing tartaric acid and a very small amount of salicylic acid as preservatives. This method of extraction is still in use in Panegrossi's hospital for encephalitis in Rome. The method is as follows:

One part of belladonna root is macerated for thirty hours in 5 parts of distilled water containing 1 per cent tartaric acid and 0.1 per cent salicylic acid, and the mixture is then percolated. A second extraction of belladonna root is carried out with the same amount of the same solvent for twenty-four hours. For better yields, a third maceration identical with the second can be done. The three extracts are mixed and filtered. The filtrate must be clear to insure stability. Finally, a solution of tartaric and salicylic acid is added to make an extract with a total alkaloid concentration of 0.02 per cent.

These are the three chief methods of extracting the active principles of belladonna root for the Bulgarian treatment. Slight modifications have been introduced, such as concentration of the extracts for more practical medication. The following method was chosen for the present study.

Cold extraction of the roots was carried out with an aqueous solvent containing 15 per cent of 95 per cent alcohol and 1 per cent of tartaric acid. The final concentration of total alkaloids was standardized by titration at 3 mg. per cubic centimeter. Repeated titration of this extract over a period of seven months revealed that even in entirely clear filtrates the alkaloid content decreases, with a minute precipitate.

Another drawback of clinical importance should be mentioned. A bottle which contains only a few cubic centimeters of the alcoholic extract and is carried in the patient's pocket may become markedly concentrated by evaporation. In several instances, some inexplicable reactions to the drug could be traced to this fact.

The choice of the belladonna roots was the most important problem. A survey of the foreign literature showed that in the early years of the Bulgarian treatment superiority was attributed to Bulgarian roots. Shortly afterward, this preference was limited to Raeff's Bulgarian roots, for other Bulgarian roots had been found less effective. Recently, the superiority of Raeff's roots gradually lost credence. Panegrossi[13] used Italian roots; Baldauf,[15] German; Kauders and Oesterreicher,[16] Austrian; Coste and Devèze,[17] French, and Neuwahl,[18] English, with identical clinical results.

I started with the use of the original Bulgarian roots, which were furnished by the successors of Raeff, in Shipka, Bulgaria. I secured an extract which produced

15. Baldauf, F.: München. med. Wchnschr. **85**:54, 1938.

16. Kauders, O., and Oesterreicher, W.: Wien. klin. Wchnschr. **49**:1548, 1936.

17. Coste, M., and Devèze, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **52**: 814, 1936.

18. Neuwahl, F. J.: Lancet **1**:693, 1939.

results identical with those obtained with acknowledged foreign extracts of Bulgarian roots, e. g. Homburg 680 (a German extract of Bulgarian belladonna root). The quality was proved by using these preparations interchangeably in treatment of the same patient.

Subsequently, I used American belladonna roots from various sources. Some of them were in bad condition, had been stored for a long time and probably were adulterated; they were less effective. Other American roots, however, proved to be equal to the original Bulgarian roots in effectiveness. This will be demonstrated in the clinical part of this study.

Different batches of roots from the same source showed slight variations in the clinical efficacy of their standardized extracts. This was true for American as well as for Bulgarian roots, and for preparations from foreign sources "standardized" according to their total alkaloid content as well as for my own extracts.

This variation is easily understood, since the standardization of extracts of belladonna root is deceptive. The amount of total alkaloids is standardized, but not the proportion of the individual alkaloids. It is obvious that roots even of an individual plant vary at different times both in their total alkaloid content and in the relationship of the different alkaloids. Variations of the total alkaloid content can easily be equalized by titration, but variations in the relationship of the individual alkaloids do not allow this standardization. This fact impairs the value of the natural extracts of belladonna root, since the value of every natural extract is problematic as long as a biologic test does not exist.

It appears that a synthetic preparation with a uniformity, stability and efficacy equal to the best natural extracts is desirable. This attempt, however, will meet the opposition of a group of investigators who believe in the superiority of the natural extract, for somewhat illogical reasons. Some of them take it for granted that the natural compound may contain an unknown substance which adds to its efficacy. Others adhere to the mysticism of "nature healing" which emanated from the Bulgarian plant collector and his miraculous method. These objections must be met with facts. The history of digitalis has illustrated how a valuable drug can be lost for a century because the varying efficacy of its natural source rendered its dosage an art of the individual physician.

The attempt to prepare a mixture of the principal alkaloids found in belladonna root had to start from clinical experience, since no biologic test was available.

Hyoscyamine, as well as atropine and scopolamine, has been used for decades in the treatment of Parkinson's disease, without satisfactory results. In this study, each of the individual alkaloids was used with a number of patients in doses as small as the content of the same alkaloid in the daily dose of extracts of belladonna root, or in doses as large as the daily dose of the entire alkaloid compound; none of them, when used alone, however, achieved the same clinical effect as extracts of Bulgarian roots.

Atropine alone in very large doses (Roemer [19]) produced generally accepted clinical results. However, those effects were obtained only with doses at least five times as large (15 mg.), and in many cases forty times as large (120 mg.), as are necessary with an alkaloid compound which will be described later. This compound, in much smaller doses, produced not only better results but also less disagreeable side effects than atropine alone.

Small, and in themselves ineffective, amounts of scopolamine were added to hyoscyamine as well as to atropine, and were tried in treatment of a group of patients. In accordance with von Witzleben's [3] observations, the patients responded better to even smaller amounts of the combined drugs than to atropine or hyoscyamine alone.

Finally, the three alkaloids hyoscyamine, scopolamine and atropine were combined. Their ratio was systematically varied, and the different combinations were tried empirically in treatment of 30 patients. The patients' subjective feelings and the objective findings were used in evaluation of the various combinations, which were given interchangeably.

So far as my present studies indicate, the range of greatest efficacy with the smallest possible dose was found with a combination of the three alkaloids in the following proportions: 75 to 95 per cent hyoscyamine, 5 to 15 per cent atropine and 1 to 5 per cent scopolamine. An empiric combination consisting of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide seemed to be particularly effective, and was preferred by 90 per cent of the patients. This alkaloid compound was made up as an aqueous-alcoholic solution containing 3 mg. of total alkaloids per cubic centimeter and 66 per cent alcohol. Tablets of identical composition were also prepared, each containing 0.5 mg. of total alkaloids. One of these tablets corresponded quantitatively with 4 or 5 drops of the aqueous-alcoholic solution.

It will be demonstrated in the clinical part of this paper that this synthetic compound proved to be of at least the same efficacy in treatment of parkinsonism as the most effective natural extracts of Bulgarian roots. On the basis of this definite clinical observation, any obscure suppositions or mystic implications about the Bulgarian treatment can be dismissed.

An average daily dose of from 2 to 3 mg. of this alkaloid compound was necessary to obtain an optimum clinical result. Since corresponding amounts of the single alkaloids were more or less ineffective, a pharmacodynamic synergism of the three alkaloids hyoscyamine, atropine and scopolamine must be assumed.

19. Roemer, C.: München. med. Wchnschr. **77**:2156, 1930; **80**:24, 1933; Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:724, 1931; Med. Klin. **28**:224, 1932.

Even with this assumption, the clinical results in parkinsonism cannot be explained. It is, of course, understood that the peripheral disturbances of the vegetative nervous system, such as hyperhidrosis and salivation, can be controlled by a compound of vagomimetic alkaloids. As to the action of the three alkaloids on the central nervous system, it is known only that atropine has a stimulating action, which may lead to excitement and hallucination. Hyoscyamine, the chief component of the compound, is less stimulating than atropine, and scopolamine has a depressing action on the central nervous system. The parkinsonian syndrome, however, is due to a chronic encephalitic process in the pallidostriatal system (substantia nigra). This disease is characterized by an unusually high tolerance for atropine, and is benefited by large doses (15 to 120 mg.) of the drug. Atropine is supposed to be pharmacologically one-half as effective as levorotatory hyoscyamine; therefore, a dose of atropine only twice that of hyoscyamine should be effective. However, it is not. The syndrome is not, or is only temporarily, influenced by small doses of atropine, hyoscyamine or scopolamine. Nevertheless, a combination of these alkaloids in a certain proportion, even in small doses, brings about striking results in postencephalitic parkinsonism. The mechanism of this effect on the central nervous system remains undetermined.

CLINICAL EFFECTS

DOSAGE

Both extracts of belladonna root and the prepared mixture of the alkaloids are powerful. Relatively small doses not only bring about striking improvement in parkinsonism, but may cause by-effects and toxic manifestations whenever the proper individual dose is surpassed. The range between the optimum effective and the toxic dose is narrow and varies with the patient. This demands careful observation and precaution in the first weeks of treatment, until the proper dose is established for the individual patient. There are few cases in which the optimum effective dose seems to coincide with the first appearance of toxic manifestations. Such effects are usually due to careless dosage rather than to real intolerance. In many patients, however, the optimum effective dose coincides with the appearance of slight by-effects. Then the patient may decide whether he prefers optimum improvement accompanied by slight by-effects or a lesser degree of improvement without by-effects. Most patients sooner or later reach the optimum result without disagreeable by-effects.

The treatment should be started with very small doses, which are gradually increased. Every other medication must be discontinued. For safety's sake, the following program is suggested.

In the treatment of paralysis agitans, the number of tablets of synthetic belladonna alkaloid compound (0.5 mg. each) given in each of three doses daily is as follows:

Day	First Dose	Second Dose	Third Dose
1	¼	¼	¼
2	¼	¼	½
3	½	¼	½
4	½	½	½
5	½	½	¾
6	¾	½	¾
7	¾	¾	¾
8	¾	¾	1
9	1	¾	1
10	1	1	1
11	1	1	1¼

In the treatment of postencephalitic parkinsonism, the number of tablets of synthetic belladonna alkaloid compound (0.5 mg. each) given in each of three doses daily is as follows:

Day	First Dose	Second Dose	Third Dose
1	¼	¼	¼
2	½	½	½
3	¾	½	¾
4	¾	¾	¾
5	1	¾	1
6	1	1	1
7	1	1	1¼
8	1¼	1	1¼
9	1¼	1¼	1¼
10	1¼	1¼	1½

In all cases, doses are further increased to the point of optimum effect and tolerance.

Quicker results are obtained by a more rapid increase in the dose, but at a greater risk of overdosage. The first appearance of by-effects, e. g., dryness of the throat, demands precaution in further increasing the dose. On the other hand, larger doses are required as long as salivation and profuse perspiration persist. Frequently one must risk some by-effects in order to obtain the best results. After several weeks of treatment the dose can often be maintained on the threshold of by-effects without impairing the therapeutic result.

The required dose must be determined for each patient. It varies from ½ to 7 tablets three times a day, but ranges on the average from 1½ to 2 tablets three times a day, or 2.25 to 3.0 mg. of total alkaloids per day. The optimum dose does not correspond with the maximum dose. When the optimum clinical result is reached, further increase approaching the maximum dose may offset the clinical effects.

The correct dose varies even in the same patient. After several months of treatment the maintenance dose can frequently be diminished without change in the patient's condition. Fever and hot weather lower the tolerance to the drug, and should be compensated for with a decrease in the dose.

The tablets are given three times a day before, or one hour after, meals. Raeff's directions prescribe only one daily dose of the extract of Bulgarian root, given at night after the first sleep. This dosage is not justified. The drug brings about only symptomatic relief for a limited time. Consequently, better results are obtained with small repeated doses. In some patients the symptoms are completely controlled with four or five doses daily; for others two doses suffice. In the majority of cases, best results are obtained with three doses daily. It is sometimes expedient to administer a somewhat larger dose at night than in the daytime. The patient when asleep is unaware of any disturbing by-effects.

Bremer [20] established the existence of a high tolerance to atropine in cases of chronic encephalitis. From 15 to 120 mg. of atropine sulfate per day can be tolerated. Patients with Parkinson's disease, however, do not show this high tolerance for belladonna alkaloid compound H or T or for the natural extracts of belladonna root. They may tolerate from two to three times as much as normal persons, but not from five to forty times as much, as is the case with atropine. This phenomenon has not been explained.

In this study, doses of from 1.25 to 10.5 mg. of belladonna alkaloid compound T were given to patients with postencephalitic parkinsonism (table 1). The average dose was 3.3 mg. Patients with nonencephalitic, i. e., degenerative or arteriosclerotic forms of Parkinson's disease (paralysis agitans) obtained optimum benefit with as little as 0.62 and as high as 3.0 mg. of belladonna compound T, the average being 1.86 mg. It is obvious that the encephalitic group required larger doses and showed a higher tolerance for the alkaloids of belladonna root. This not only is important for the therapeutic management of the patient, but may also be significant in differential diagnosis of the encephalitic and the nonencephalitic variety of the disease. None of the patients with degenerative or arteriosclerotic parkinsonism required more than 3 mg. of total alkaloids per day. Most of these patients reached the optimum effect with much smaller doses, and showed a low tolerance for the drug. Since some patients with postencephalitic parkinsonism deny that any acute episode of encephalitis has occurred in their history, a relatively high tolerance and a high alkaloid requirement may reveal the real nature of the disease.

By-effects occur less frequently and are less pronounced with belladonna alkaloid compound T or with extracts of belladonna root than with large doses of atropine. The main reason is the difference in dosage. Dryness of the mouth usually appears earlier than mydriasis and blurred vision, which are relatively rare. Both are more frequent and more marked in the first weeks of treatment than in later stages,

20. Bremer, F. W.: Deutsches Arch. f. klin. Med. **149**:340, 1925.

TABLE 1.—*Data on Effects of Treatment of Parkinsonism with Belladonna Alkaloid Mixture T*

Case No.	Age, Yr.	Duration of Disease, Yr.	Severity of Disease	Result of Treatment	Ability to Work, Percentage	Duration of Treatment	Maintenance Dose of Belladonna Alkaloid Compound T, per Day, Mg.	By-Effects and Toxicity
				I. Postencephalitic Parkinsonism				
1	27	½	Moderate	Markedly improved	100	4 mo.	2.0	Slightly dry throat
2	38	1½	Mild	Markedly improved	100	1½ mo.	3.0	Slightly dry throat
3	51	1½	Moderate	Markedly improved	90	4½ mo.	3.0	Slightly dry throat
4	25	2	Moderate	Markedly improved	100	3½ mo.	3.5	None
5	42	2	Moderate	Markedly improved	100	½ mo.	(1.8)	None
6	32	2	Mild	Markedly improved	100	5 wk.	2.75	Slightly dry throat
7	41	2½	Mild	Slightly improved	100	2 mo.	3.5	Occasionally dry throat
8	36	3	Moderate	Markedly improved	100	6 mo.	2.25	Occasionally dry throat
9	32	4	Moderate	Moderately improved	80	4 mo.	...	
10	43	4	Severe	Moderately improved	50	3 mo.	3.0	None
11	50	4	Severe	Markedly improved	50	3 mo.	10.5	None
12	56	4	Moderate	Moderately improved	100	3 mo.	2.0	Slightly dry throat
13	34	5	Moderate	Treatment discontinued	...	3 days	1.25	None
14	23	5	Moderate	Markedly improved	100	14 mo.	3.5	Slightly dry throat
15	42	5½	Severe	Markedly improved	50	3 mo.	4.25	Slightly dry throat
16	36	6	Severe	Markedly improved	80	4½ mo.	(4.5)	None
17	25	6	Mild	Markedly improved	100	1½ mo.	7.5	None
18	30	6	Moderate	Markedly improved	100	3½ mo.	2.75	Dry throat; blurred vision
19	39	6	Severe	Slightly improved	70	4½ mo.	2.25	Slightly dry throat
20	38	6½	Moderate	Markedly improved	100	4 mo.	3.0	None
21	44	7	Moderate	Moderately improved	90	3½ mo.	(4.5)	None
22	45	7	Severe	Moderately improved	60	1 mo.	2.0	Dry throat
23	54	7	Severe	Markedly improved	50	2 mo.	7.5	None
24	42	9	Severe	Slightly improved	70	1½ mo.	3.0	Dry throat
25	35	9	Moderate	Moderately improved	100	4½ mo.	2.0	None
26	41	9	Moderate	Moderately improved	100	5 mo.	3.0	None
27	59	10	Severe	Moderately improved	50	3 wk.	(3.0)	Dry throat; blurred vision
28	40	11	Moderate	Slightly improved	80	7 mo.	2.25	None
29	34	11	Moderate	Moderately improved	80	½ mo.	3.0	Moderately dry throat
30	28	12	Severe	Markedly improved	70	1½ mo.	2.5	Dry throat; blurred vision
31	39	13	Moderate	Moderately improved	80	4 mo.	(1.0)	Slightly dry throat
32	29	16	Severe	Moderately improved	0	2 wk.	(2.0)	None
33	49	16	Severe	Moderately improved	50	2 wk.	4.0	None
34	49	19	Severe	Unimproved	50	3 wk.	(1.5)	Dry throat; blurred vision
				II. Nonencephalitic Parkinsonism				
1	49	1	Moderate	Moderately improved	40	4½ mo.	3.0	Dry throat
2	52	10 weeks	Mild	Markedly improved	100	3½ mo.	2.25	None
3	52	5	Moderate	Unimproved	60	3 mo.	1.5	None
4	55	7 weeks	Moderate	Moderately improved	80	2 mo.	2.5	Slightly dry throat
5	56	3	Moderate	Slightly improved	..	4 mo.	1.5	Slightly dry throat
6	57	3	Moderate	Slightly improved	90	1½ mo.	(1.0)	Excitement (psychic ?)
7	57	7	Mild	Markedly improved	100	2 mo.	0.62	None
8	58	4	Mild	Moderately improved	70	2 mo.	2.0	Moderately dry throat
9	59	4	Severe	Slightly improved	..	½ mo.	(1.0)	Slightly dry throat
10	61	7	Moderate	Slightly improved	..	4 mo.	2.5	Slightly dry throat
11	62	2½	Severe	Slightly improved	..	5 mo.	1.0	Slightly dry throat
12	64	1½	Mild	Markedly improved	..	3½ mo.	1.5	Slightly dry throat
13	64	1	Moderate	Moderately improved	..	4 mo.	2.0	None
14	65	2	Moderate	Moderately improved	80	4 mo.	3.0	Slightly dry throat
15	70	5	Mild	Moderately improved	90	7½ mo.	0.75	None
16	70	20	Moderate	Unimproved	..	4 mo.	2.0	Slightly dry throat
17	72	7	Mild	Unimproved	..	1 mo.	1.8	Slightly dry throat
18	77	3	Severe	Slightly improved	0	1 mo.	(1.5)	None

when the patient has become accustomed to the drug and the dose can be lowered. After about three months' treatment the dose can usually be regulated so as to avoid any disagreeable by-effect. Calmus root, which was recommended by Raeff, does not materially relieve the dryness of the throat; most patients prefer chewing gum. Instillations of pilocarpine do not counteract the mydriasis.

In the first period of treatment slight gastrointestinal disturbances and difficulty in urination may occur. This can be corrected by decreasing the dose. Constipation is rare; preexistent spastic constipation may even be relieved by the drug. Vague sensations in the region of the stomach are probably due to gastric hypoacidity, and can be counteracted by dilute hydrochloric acid. Severe damage, which has been described as following prolonged use of large doses of atropine, need not be feared with the small doses of belladonna alkaloid mixture, and has not been actually observed.

Toxic manifestations can be completely avoided with proper dosage. Excitement, delirium and hallucinations, such as were described with large doses of atropine as well as in Raeff's treatment with unstandardized decoctions of belladonna root, have not been observed during treatment with the belladonna alkaloid mixture. Slight dizziness or a feeling of sluggishness are occasionally described by the patients; these are signs of overdosage.

CLINICAL RESPONSE TO THE ALKALOIDS OF BELLADONNA ROOT

Not all symptoms of the disease respond to the drug simultaneously or to the same extent. Improvement of the various symptoms follows the same order in almost every patient. General spirits and muscular rigidity are the first to respond with striking improvement within one or two weeks. Some patients seem to become worse during the first few days of treatment, because a previous medicament, e. g., atropine or scopolamine in large doses, has been discontinued and the new drug has not yet reached an effective level in the blood. In such cases the treatment can be started with larger doses. However, in general, the patients return after the first period of treatment with such enthusiastic utterances as: "I am an entirely new person"; "I feel 1,000 per cent better"; "That is a wonderful medicine." Most of them say that it is the best medicine they ever had. The initial success and overenthusiasm sometimes are followed by "relapses" in the succeeding weeks. These relapses are chiefly psychic, and are due to dissappointment when the progress slows or becomes stationary in the later period of treatment. Some patients expect too much and anticipate a complete cure. Others are discouraged by the fact that the drug must be administered permanently and brings about only symptomatic improvement. They do not grasp this fact, and they do not want to. Resulting

disappointment must be overcome by reassurrance. Progressive improvement may continue for many months, until the optimum is reached.

The psychic state not only may be markedly improved by the medication, but also may interfere with its effect. Psychic symptoms which usually accompany Parkinson's disease, such as weakness, inner tension, restlessness, reactive depression or despair, respond favorably to the drug. On the other hand, every episode of excitement or psychic instability may reproduce symptoms which were previously controlled.

A patient with severe postencephalitic parkinsonism was markedly improved and lost almost all his symptoms after several weeks of treatment. Without any change in the dose of the drug, the patient had a relapse a few weeks later. Psychic exploration revealed tension between the patient and his brother, of whom he had always spoken highly. Dis-

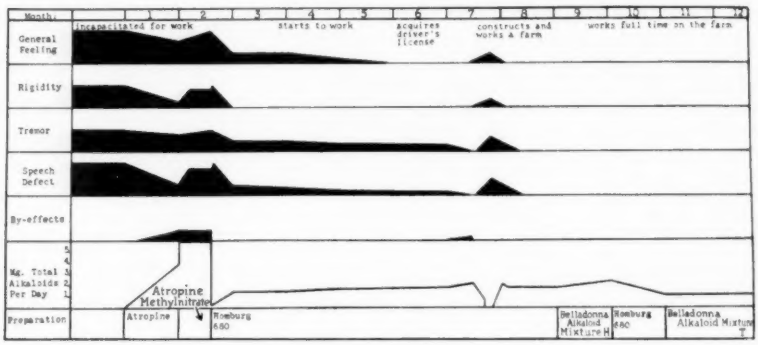

Fig. 1.—E. H., a man aged 22, with postencephalitic parkinsonism of five years' duration, showed slight improvement with atropine, but obtained complete relief from his symptoms after seven months' treatment with belladonna root alkaloids. Formerly completely incapacitated, he now works full time on a farm. When the treatment was discontinued in the seventh month, the symptoms were not as severe as before treatment.

cussion of the situation brought about mental catharsis, and the former improvement in the symptoms reappeared.

Parkinsonian patients seem to have common psychic characteristics. They are sensitive, good natured, trustful and thankful, and have a strong desire to get well. They are cooperative and follow every direction carefully. It is important to encourage them until an obvious clinical result is obtained. Hopelessness and skepticism delay the objective improvement.

Figures 1 to 8 illustrate the course of improvement in 8 cases. In these figures, the height of the black curves indicate the severity of the symptoms. It is obvious that muscular rigidity, including amimic, bradykinetic, catatonic and cataleptic symptoms, shows most improve-

ment and quickest response to the treatment. In most patients muscular rigidity can be completely controlled within two to four weeks. That may explain in part the favorable psychologic reaction of the patients on obtaining relief. At the same time, muscle spasms, muscle pain and

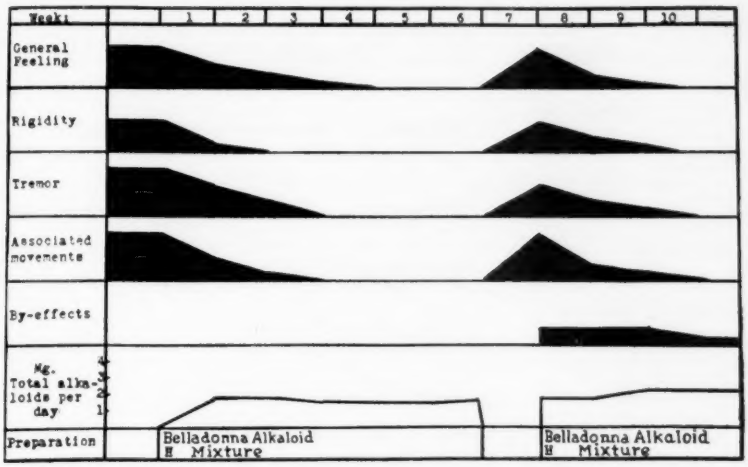

Fig. 2.—S. G., a concert singer aged 52, who had had parkinsonism, of unknown origin, for ten weeks, lost all symptoms after treatment with belladonna alkaloid, mixture H, for four weeks and was able to go on a concert tour. His symptoms recurred in the seventh week, when he ran short of the drug.

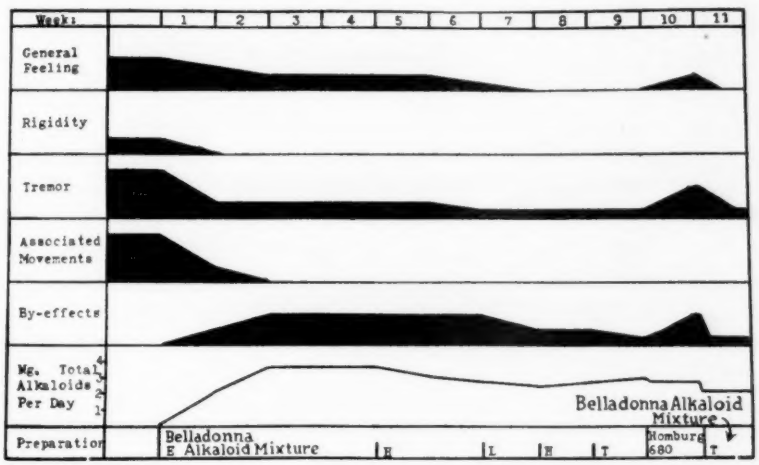

Fig. 3.—F. B., a woman aged 38, had had postencephalitic parkinsonism for six and a half years. Rigidity disappeared after one week of treatment with belladonna alkaloid compound T; the associated movements reappeared after two weeks' treatment. Tremor was decreased, and on occasions was completely absent. The synthetic alkaloid compound was more effective than Homburg 680.

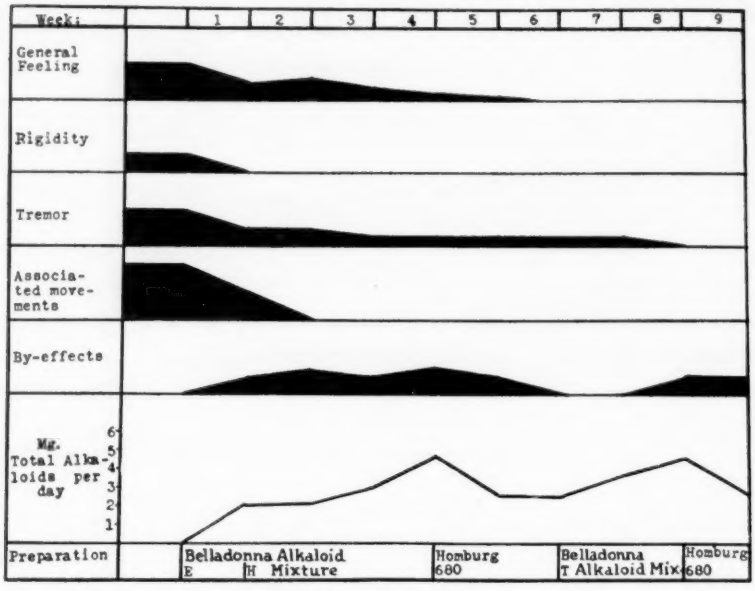

Fig. 4.—M. R., a woman aged 25, with postencephalitic parkinsonism of two years' duration, became entirely free from symptoms after treatment for eight weeks.

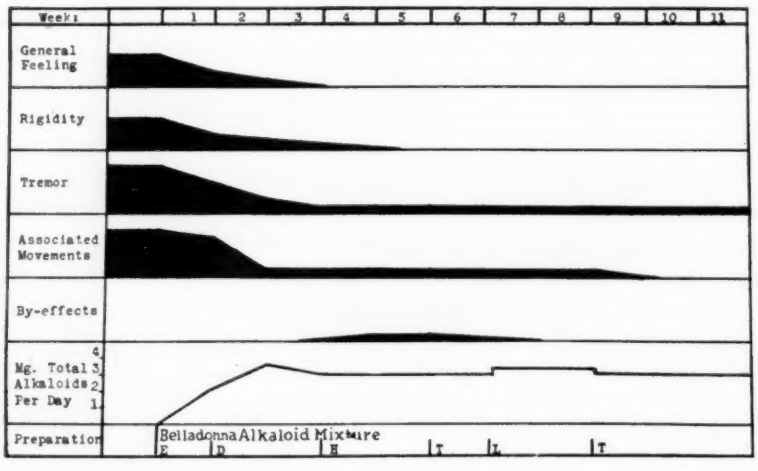

Fig. 5.—T. H., aged 51, had had paralysis agitans, of unknown origin, for one and a half years. The general spirits and rigidity were the first to improve under treatment with belladonna alkaloid mixture. The associated movements reappeared after nine weeks' treatment. Tremor was not completely controlled.

disturbances in speech and handwriting are markedly improved. Samples of handwriting (figs. 9 to 15) impressively demonstrate the progress.

With the disappearance of muscular rigidity the patients regain power in their limbs. They lose the "weakness," become more active

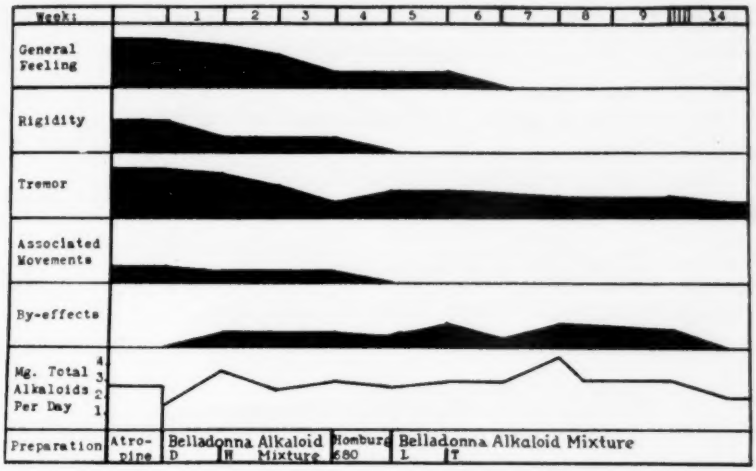

Fig. 6.—The chart for J. S., aged 44 years, with postencephalitic parkinsonism of seven years' duration, illustrates the superiority of the belladonna root alkaloids over atropine. All symptoms disappeared except the tremor, which was only moderately improved.

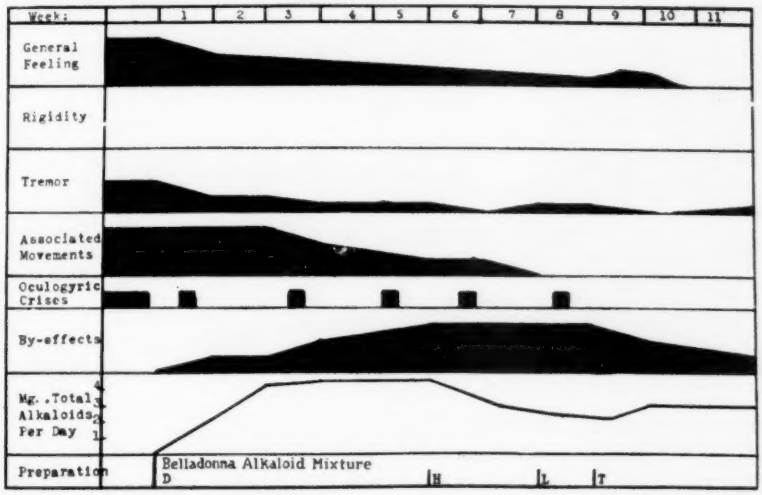

Fig. 7.—A. S., a woman aged 27, with postencephalitic parkinsonism of six months' duration, had marked improvement in the oculogyric crises with belladonna alkaloid mixture T.

and desire to use their regained power in gradually increasing activities. They walk faster, arise more easily from a sitting position and have less difficulty in turning while recumbent. Lost abilities, such as buttoning a suit, tying shoelaces, winding a watch or picking up tiny objects, are gradually regained.

Frequently, most of the muscular rigidity has disappeared before the masklike facies changes to a more lively expression and the associated movements reappear.

Secretory disturbances, such as sialorrhea and hyperhidrosis, can always be completely controlled by the proper dosage. These symptoms

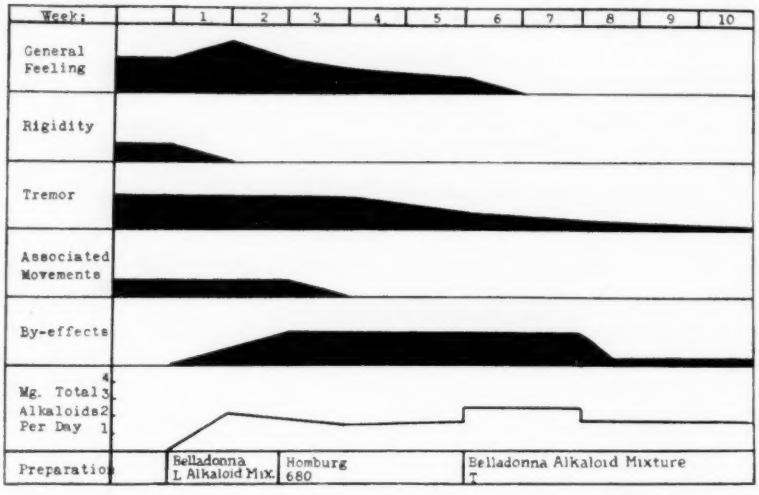

Fig. 8.—Chart for M. W., aged 58, with parkinsonism of unknown origin, of four years' duration.

may be a valuable guide for establishment of the optimum dose. As long as they persist, the dose may be increased without risk.

The hyperkinetic symptoms do not respond as well and as quickly as the muscular rigidity. Patients with an advanced form of the disease are rarely completely relieved from the tremor. Nevertheless, even in the later stages the tremor becomes less violent and its vibrations are slower. This improvement manifests itself in recovery of ability to eat alone and to use a spoon without spilling the food. In many cases of the early stage the tremor is completely controlled. It seems that the tremor in the various extremities disappears in the reverse order of its appearance; i. e., tremor in the part which was involved last is the first to be relieved.

During the course of the day the tremor shows changes in intensity. It depends not merely on the emotional state of the patient, but also on the action of the drug. In many cases, from one to three hours after

the administration of the drug the tremor stops completely for one or more hours, and then reappears. Adaptation of the dose to the individual response may result in continuous and even relief of the tremor.

The handwriting reflects better than oscillographic records the combination of tremor and rigidity. It is striking to see complete inability to write for seven years (fig. 9) give way to ability to write fairly well after a few days of treatment. More subtle analysis of the samples of handwriting (figs. 9 to 15) reveals not only the decrease in frequency and amplitude of vibrations but also the more fluent ductus, the diminished inhibition and the greater firmness in the letters.

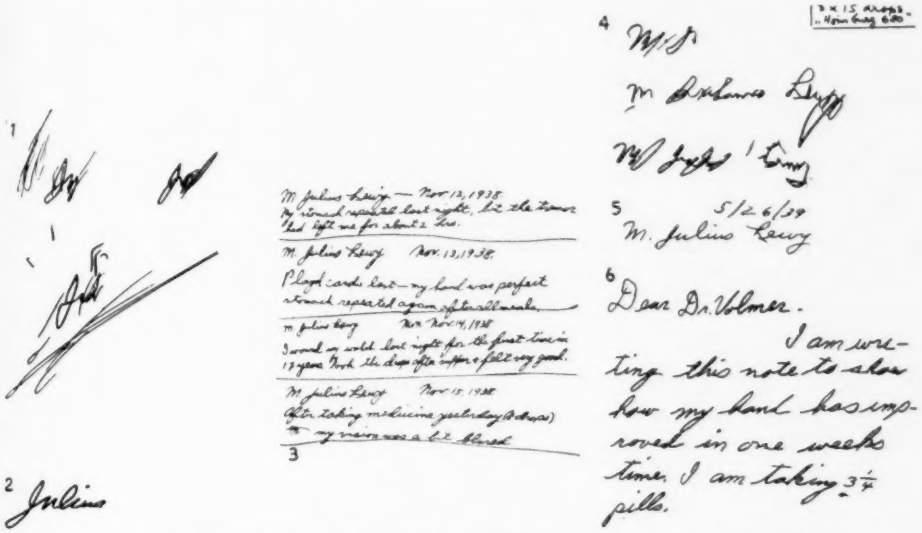

Fig. 9.—Handwriting of a patient with postencephalitic parkinsonism who had been unable to write his name (*1*) for seven years. He regained ability to write after treatment with belladonna root extracts for one week. (*2*) was obtained after six days' treatment (Nov. 11, 1938), and (*3*) after seven to ten days' treatment.

Extracts of Bulgarian belladonna root (Raeff) proved to be less effective than extracts of American roots. (*4*) shows the writing four months later (March 14, 1939) after the patient took an extract of Bulgarian root (Homburg 680), and (*5*), about two months later (May 26), after an extract of American belladonna root. Belladonna alkaloid compound T (4.9 mg. daily) showed the same effect on the handwriting (*6*, taken Aug. 7, 1939), as the most effective natural extracts of belladonna root.

A similar improvement of speech may be observed. The typical hesitation in beginning speech and the subsequent hurry to complete it, as well as stuttering, disappear in many cases. A concert singer (fig. 2) who was unable to sing before the treatment went on a concert tour and did well after four weeks' treatment. The monotonous speech in cases of advanced disease, however, frequently resists therapy.

Oculogyric crises, one of the most distressing symptoms, are definitely improved. They become less violent and less frequent with the treatment. A patient (fig. 7) who had suffered from daily crises

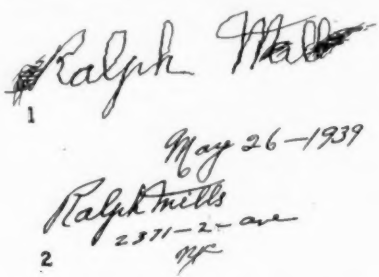

Fig. 10.—This chart demonstrates the marked improvement in the handwriting of a patient with postencephalitic parkinsonism after treatment with the synthetic belladonna alkaloid compound. It took three minutes to write the first sample (*1*), before treatment, but only fourteen seconds to write the second (*2*), after treatment.

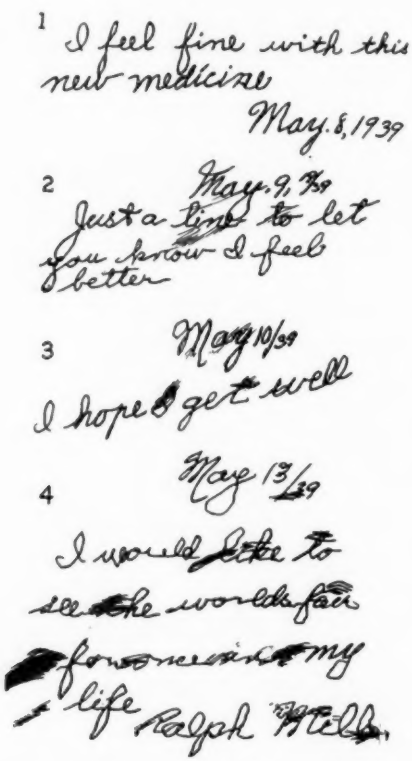

Fig. 11.—Handwriting of the same patient whose writing is shown in figure 10. The writing gradually deteriorated when treatment was stopped for one day (*1*), for two days (*2*), for three days (*3*) and for six days (*4*).

before the treatment had only two or three episodes a month with treatment. In none of 3 cases were the crises completely eliminated.

Sleep is improved in a high percentage of patients. Especially in the restless and tense type of parkinsonism, the patient not only is quieter in the daytime but sleeps more soundly and longer at night.

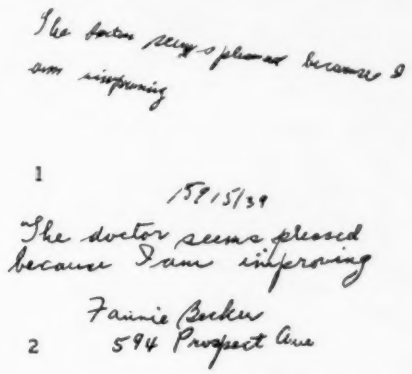

Fig. 12.—This chart demonstrates the marked improvement in the handwriting of a patient with postencephalitic parkinsonism after treatment (*2*) for one week with belladonna alkaloid compound. *1* was taken before treatment.

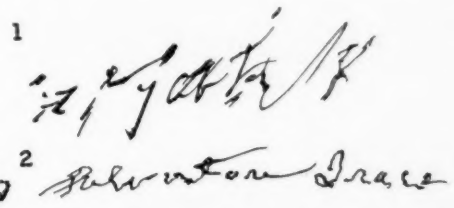

Fig. 13.—Handwriting of a patient aged 55 with paralysis agitans before treatment (*1*), and after eight weeks of treatment with synthetic belladonna alkaloid compound (*2*).

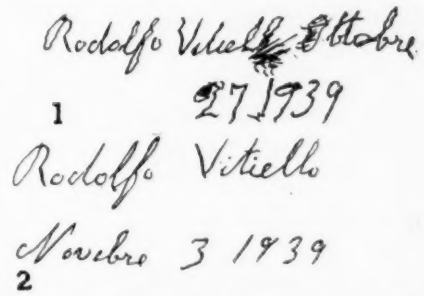

Fig. 14.—Handwriting of a patient aged 59 with postencephalitic parkinsonism of ten years' duration. *1* was taken before treatment; *2* shows the marked improvement of the handwriting after seven days' treatment with synthetic belladonna alkaloid compound.

When the treatment is discontinued all symptoms recur. It is noteworthy, however, that three days may elapse before the condition of the patients becomes worse. Response to treatment with large doses of atropine does not persist in the same manner.

Another observation is of great interest. Parkinson's disease is progressive. Nevertheless, few patients who had been treated for many months and whose medication was stopped showed symptoms as severe or fully developed as before therapy. The first patient, who received treatment for fourteen months and became practically symptom free (fig. 1), was definitely improved even after the treatment was discontinued for two weeks. However, the period of observation of my patients is too short to permit a final statement. In what manner these alkaloids affect the involved parts of the brain remains to be determined.

Fig. 15.—Handwriting of a patient aged 54 with encephalitis, demonstrating the superiority of smaller doses of synthetic belladonna alkaloid compound over larger doses of scopolamine hydrobromide alone.

RESULTS OF TREATMENT

Fifty-two patients were treated, 34 of whom had postencephalitic parkinsonism and 18 nonencephalitic paralysis agitans. This classification is necessary, because the response to the drug is more favorable in the group with the postencephalitic form than in the group with the degenerative or arteriosclerotic form.

Table 1 contains data on both groups. The postencephalitic patients are tabulated in the order of duration of the disease; the nonencephalitic patients, according to age. The therapeutic results depend on both factors, but chiefly on the duration of the disease in the encephalitic group and on the age of the patient in the nonencephalitic group. However, there is no infallible rule for prognosis. One cannot predict which patient will be benefited and which will not. Generally the outlook is

best for young patients with postencephalitic parkinsonism of short duration; they usually become free from symptoms and entirely able to work. On the other hand, the prognosis is poor for elderly patients with paralysis agitans of long duration. Three patients of the second group (table 1, patients 3, 16 and 17) were not benefited by the treatment.

A high percentage of patients of the postencephalitic group regain the capacity to work. In table 1 the ability to work is recorded in terms of work actually done by the patient; in case of unemployment this ability had to be estimated. It is obvious that the encephalitic group exhibited better results in this respect. In the arteriosclerotic group it was often difficult to determine whether the disease or the patient's age was the chief reason for inability to work; many figures have, therefore, been omitted.

TABLE 2.—*Comparison of Results of Bulgarian Treatment of Postencephalitic Parkinsonism and of Paralysis Agitans*

Result	Postencephalitic Parkinsonism		Paralysis Agitans	
	Patients	Percentage	Patients	Percentage
Markedly improved	17	50	3	17
Moderately improved	11	32	6	33
Slightly improved	4	12	6	33
Unimproved	1	3	3	17
Treatment discontinued	1	3	0	0

In table 2 the patients of both groups are listed according to the degree of improvement. Fifty per cent of the postencephalitic, but only 17 per cent of the nonencephalitic, patients were markedly improved. The 4 patients who became entirely free from symptoms had chronic encephalitis. In this group the treatment may completely change the life of the patient (fig. 1). In the case of nonencephalitic patients only partial relief can be expected. Nevertheless, even this limited improvement may turn a complete invalid into a person who can enjoy some degree of independence and take part in some activities.

EVALUATION OF SYNTHETIC BELLADONA ALKALOID COMPOUNDS

The advantages of a stable and uniform synthetic preparation previously mentioned do not warrant its clinical use unless it is as effective as natural extracts. Such effectiveness must be judged by subjective reports as well as by objective findings. The judgment of the patient is not necessarily to be trusted. Most patients have been treated for years with various preparations, with limited success. Once they note definite improvement with a "new" medicine, they wish to continue with the same drug. They distrust any change. Consequently, most patients like only the first medicine from which they receive benefit.

Since the natural as well as the various synthetic alkaloid compounds were administered in solution to most patients before the tablets were prepared, the latter frequently met with resistance on the part of the patients—for example, "I took pills for years, and they did not help me; I want the drops."

Nevertheless, the tablets were given to 31 patients interchangeably with extracts of belladonna root and a solution of the belladonna alkaloid compound. After several weeks or months of experience, 21 patients declared preference for the tablets, 5 did not like them and 5 found their effectiveness equivalent to that of the other preparations.

This favorable subjective response was confirmed by objective observation. The following preparations, which are mentioned in figures 1 to 8, were used interchangeably in treatment.

Homburg 680: A German extract of Bulgarian belladonna root, containing 3 mg. of total alkaloids per cubic centimeter.

Belladonna alkaloid mixture C: Acid-alcohol extract of American belladonna root, containing 2 mg. of alkaloids per cubic centimeter.

Belladonna alkaloid mixture D: Acid-alcohol extract of Bulgarian belladonna root obtained from the successors of Ivan Raeff, Shipka, Bulgaria, containing 2.39 mg. of total alkaloids per cubic centimeter of 15 per cent alcohol.

Belladonna alkaloid mixture E, F, G and L: Extracts of American belladonna root, prepared like belladonna alkaloid mixture D, but containing 3 mg. of alkaloids per cubic centimeter of 66 per cent alcohol.

Belladonna alkaloid mixture H: Synthetic preparation, containing 3 mg. of total alkaloids per cubic centimeter of 66 per cent alcohol in the following proportions: 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide.

Belladonna alkaloid mixture T:[21] Tablets, each containing 0.5 mg. of alkaloids in the same proportion as in mixture H.

Of the natural extracts, belladonna alkaloid mixtures D, G and L and Homburg 680 proved to be effective. The synthetic compounds and these natural preparations were administered interchangeably, in most cases repeatedly, and were compared as to efficacy. Each period of comparison lasted from one to several weeks.

A careful analysis of all cases leads to the following conclusion: In some cases, e. g. case 20 (fig. 3), the synthetic tablets proved to be definitely superior; in all others there was no appreciable difference in the efficacy of these tablets and that of the most effective natural extracts.

It was noted further that the synthetic alkaloid compound was far more effective and less dangerous than large doses of atropine. Since megacolon has been described in the literature[3] as a result of prolonged

21. Rabellon, manufactured by Sharp & Dohme.

administration of large doses of atropine, treatment with this drug should be abandoned.

CONTRAINDICATIONS

The advanced age of the patient or the long duration and progression of the disease are not contraindications to the treatment with belladonna alkaloid mixtures. Careful dosage is necessary in these cases, but unexpected improvement may occur.

According to von Witzleben [3] and Neuwahl,[18] the treatment is contraindicated in cases of low body weight and of such conditions as myocardial disease, disease of the kidney or liver, diabetes, tuberculosis, glaucoma, severe anemia, epilepsy and prostatic hypertrophy. Patients with acute encephalitis are unsuitable for treatment. Von Witzleben [3] recommended discontinuation of treatment if it causes repeated psychic disturbances which previously did not exist. Psychic disorders which are due to the encephalitic process and existed before the treatment, however, are not a contraindication.

My experience did not contribute to the solution of this question. There were only 2 patients, with asthma and diabetes, respectively, in whose cases the question of contraindication had to be considered. Both tolerated the drug well.

SUPPLEMENTARY THERAPY

Raeff recommended a special diet: Meat, except white, should be avoided. The diet should be mixed and should consist chiefly of eggs, milk, butter, cheese, vegetables, fruits, rice, olives, cakes and candies. Panegrossi,[13] as well as von Witzleben,[3] followed this regimen in their institutions. In my experience it has no special virtue. It is possible, however, that dietetic restrictions may have a psychotherapeutic effect on some patients. I eliminated only tobacco, alcohol and coffee, as recommended by Raeff. This seems to be as important in management of parkinsonism as in that of any other disease of the nervous system.

Von Witzleben [3] stressed the importance of exercise. It may be true that this is of value. The patient should be encouraged to increase his radius of activity gradually, in walks as well as in daily work. A group of patients who took special exercises showed no additional benefit.

Psychotherapy is undoubtedly valuable. This has been stressed previously in this paper. Psychotherapy may be well disguised, as it probably was in Panegrossi's and in von Witzleben's treatment. Their patients were hospitalized in beautiful institutions. This meant to most of them a change from poor and dismal conditions to sumptuous and quiet surroundings. Previously criticized or nagged within the family, they were taken care of with sympathetic understanding in the hospital. These improved conditions are undoubtedly valuable, and help to overcome the despair of many patients.

My patients did not have these advantages of hospitalization and special care. They were treated in the neurologic clinic and remained in their original environments, which were unfavorable in many cases. Hopelessness may develop as a result of the long, progressive disease. It is essential to change this negativistic attitude. Extensive psychotherapy is rarely necessary. An encouraging word often suffices to improve the patient's spirits, while physical improvement proceeds as a result of the medication.

SUMMARY

The effect of the Bulgarian treatment on Parkinson's disease is due to the alkaloids in the belladonna root.

The pharmacologic characteristics of these roots, their alkaloids and their extracts, are described.

A synthetic compound was prepared consisting of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide.

The therapeutic effect of this synthetic preparation is ascribed to a pharmacodynamic synergism of hyoscyamine, atropine and scopolamine when combined in a certain proportion.[22]

This synthetic compound is stable and uniform, and therapeutically is at least equivalent to the most effective natural extracts.

The optimum dose must be established for each patient. It is higher for persons with postencephalitic parkinsonism than for those with paralysis agitans. The average daily dose for patients of the former group was 3.3 mg. and that for the latter, 1.86 mg.

Postencephalitic parkinsonism responds better than paralysis agitans to the belladonna alkaloid compound.

The difference in response of the various symptoms to the drug is described.

Of 34 patients with postencephalitis, 50 per cent were markedly improved and 32 per cent were only moderately improved. Some of them became free from symptoms, and the majority were able to work.

Of 18 patients with paralysis agitans, only 17 per cent were markedly improved and 33 per cent were moderately improved.

Treatment with the belladonna alkaloid compound is symptomatic, and must be continued indefinitely.

The contraindications and the value of supplementary psychotherapy are discussed.

Dr. I. S. Wechsler furnished the opportunity to carry out this study; Dr. Bertram Schaffner helped in editing the manuscript, and the research department of Sharp & Dohme, Philadelphia, furnished all preparations used in the study.

25 Central Park West.

22. Much work is yet necessary to determine whether this ratio of alkaloids is the best ratio and whether all three alkaloids are needed.

PERSONALITY CHANGES ACCOMPANYING CEREBRAL LESIONS

II. RORSCHACH STUDIES OF PATIENTS WITH FOCAL EPILEPSY

M. R. HARROWER-ERICKSON, PH.D.
MONTREAL, CANADA

In part I of this study [1] the Rorschach method was used as a means of estimating the "changed" personality of patients with cerebral tumors. After a comparatively uniform and typical record had been found in a study of 28 preoperative and postoperative records of patients with verified lesions, a composite psychogram from such records was used as a standard, with which the psychograms of clinical "tumor suspects" were compared. Examples were given of records which fell easily under the type characteristic of persons with cerebral lesions and of those which could not be so classified. The Rorschach diagnoses were verified clinically. Three possible explanations of the personality changes were considered.

The present study of patients with focal epilepsy attempts to answer several of the questions raised in part I and left undecided by consideration only of patients with cerebral tumors. Such questions are: 1. Must all types of cortical damage be reflected in the same kind of deviation from the normal Rorschach record? More specifically, will the presence of scar tissue, small areas of atrophied brain or microgyria, such as are found in some patients with focal epilepsy, inevitably result in a preoperative Rorschach psychogram similar to the preoperative psychogram of the patient with tumor? 2. Will all "cortical removals," regardless of the remaining pathologic alterations, result in a picture similar to the postoperative picture in cases of tumor? Will the postoperative records in cases of focal (traumatic) epilepsy in which clean surgical removal has been achieved still give the uniform and restricted picture which one associates with the widespread type of cerebral lesion discussed in part I? 3. What of the "epileptic personality"? Has such a term any validity as applied to patients with focal epilepsy when considered from the Rorschach standpoint? Are there typical records with group characteristics, such as have already been found for patients

From the Department of Neurology and Neurosurgery, Montreal Neurological Institute and McGill University.

1. Harrower-Erickson, M. R.: Personality Changes Accompanying Cerebral Lesions: I. Rorschach Studies of Patients with Cerebral Tumors, Arch. Neurol. & Psychiat. **43**:859 (May) 1940.

with established cerebral neoplasms, on the one hand, and as Stauder [2] has found for deteriorated patients with "genuine" epilepsy, on the other?

MATERIAL

The records which are now to be discussed were taken from 24 patients with focal epilepsy, all of whom were operated on for the removal of scar tissue or areas of atrophy or microgyria. The removals varied from bilateral frontal lobectomy (case 12) to what was "almost a negative exploration" in the left temporal region (case 7).

These 24 patients have been divided into three groups. Group A consisted of 10 patients who were tested before and again after operation, just before leaving the hospital, that is, after approximately six weeks. Group B consisted of 4 patients who were tested postoperatively and again one year later. The first postoperative records were taken at various intervals after operation. Group C, the records of which will not be discussed in detail, consisted of 10 patients tested once postoperatively, thereby constituting a "control" group in the sense that any possible practice factor was eliminated.

Location of Lesions.—Group A.: In the 10 cases in which both preoperative and postoperative studies were made, the removals of tissue were from the following areas: frontal, 3 cases; frontoparietal, 1 case; parietal, 2 cases, and temporal, 4 cases.

Group B.: In the cases in which two postoperative studies were made, the distribution was: frontal area, 3 cases (1 bilateral), and parietal, 1 case.

Group C.: In the cases in which only one postoperative study was made, the locations were: frontal, 3 cases; parietal, 4 cases; temporal, 2 cases, and occipital, 1 case.

In addition to these preoperative and postoperative studies, psychograms are presented which illustrate the effects of medication on different types of records. Examples are given of records from deteriorated and nondeteriorated epileptic patients, when receiving and when not receiving medication. Also included are the records of 4 patients who had "negative exploration" which serve as a basis of comparison for the records both of the patients with focal epilepsy and of those with lesions considered in part I.

It will be remembered that in considering the records of the patients with tumor sufficient similarity was found to enable one to make a composite picture and to compare this with a similar picture made from the records of a group of average normal persons, and that marked differences were apparent. The fact that a corresponding composite picture made from the records of patients with focal epilepsy does not provide such a contrast with the normal is in itself an indication that the "epileptic personality" does not emerge in this way. Nevertheless, many points of interest would be masked if the matter were allowed to rest with the statement that there is nothing grossly different between a composite picture of patients with focal epilepsy and one of normal persons. I have therefore considered 14 of these 24 records individually, partly to bring out their diversity and lack of conformity to a basic pattern and partly because the composite picture gives too simplified an impression and does not indicate the individual abnormalities and changes which make these records of particular interest and value. For the

2. Stauder, K. H.: Konstitution und Wesensänderung der Epileptiker, Leipzig, Georg Thieme, 1938.

composite records of the normal persons (fig. 2, part I) and of the 28 patients with gross lesions (fig. 7, part I), which will serve as a basis of comparison for the psychograms which follow, as well as a detailed description of how these psychograms are derived from the records, the reader is referred to part I of this study.[1]

PSYCHOGRAMS

GROUP A: *Patients Studied Preoperatively and Postoperatively.*—In considering this group, I am interested chiefly in (*a*) a comparison

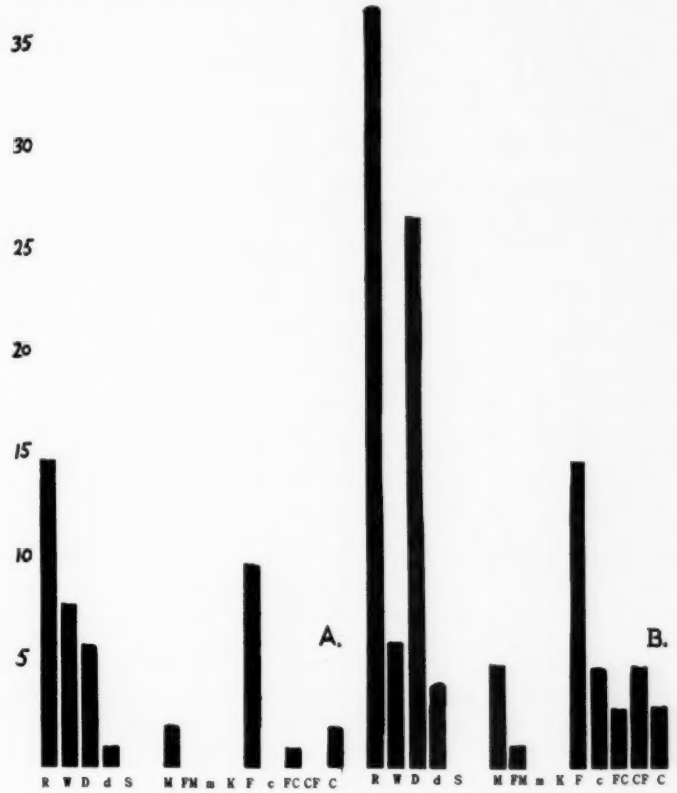

Fig. 1.—Preoperative (*A*) and postoperative (*B*) records in case 1.

between the preoperative and the postoperative records of each patient and (*b*) a search for possible similarities among all the preoperative and all the postoperative records. Summaries of the cases follow.

CASE 1.—The patient was a woman aged 28.

In his operative notes, Dr. Wilder Penfield stated: "A large scar from an old abscess of the brain was present in the right temporal lobe. The superficial lesion and adhesions were in the postcentral face area. The removal was a wide one, as it seemed wise to excise the area from which the aura was obtained and also the large lesion."

The first Rorschach record was made before operation; the second, six weeks after operation, when no abnormal waves were found in the electroencephalogram. Before operation this patient had had difficulty in the wards and had been much given to criticism and querulousness. After operation she was much more cooperative and friendly.

If one compares the two psychograms in figure 1, it is obvious that a marked psychologic change has occurred. If one assumes for the moment that the postoperative record approximates the normal basic personality of this patient (since it was taken at a time when abnormal waves in the electroencephalogram had ceased), one must see the preoperative psychogram as influenced in the direction of the constricted type of record which was found to be indicative of cerebral dysfunction produced by tumor. That it is not the typical constricted record of the cerebral damage produced by neoplasm, however, is seen in several ways: in the unusually high percentage of *F* plus responses and in the fact that this is the record of a basically extrovert personality with an $M:\Sigma C$ ratio of $2:4$. The 2 pure *C* responses, unsupported by *FC* or *CF* responses and not offset by sufficient *M* responses, are indicative of the explosiveness of the patient's emotions.

Record *B* shows a reversal of the $W:D:d$ ratio which is startling and an increase to 5 *M* responses. The affective responses now include 3 of the *FC* and 5 of the *CF* type, in addition to the pure *C* type. There is also the addition of 5 *c* responses, which, in view of the changed overt behavior, can be interpreted as indicating greater approachability and sensitivity to others. The ratio of $M:\Sigma C$ is now $5:12$; i. e., the patient is still basically an extrovertive, dilated personality, but she is functioning now in a fuller and more adequate way. Since this change occurred within six weeks, before it could be known whether or not she was physically permanently cured it would seem as if there were certain purely psychologic handicaps and barriers inherent in the total situation associated with the convulsions which were in a sense benefited by operation. It would seem as if this essentially extrovert personality had been impeded in much needed normal contacts with other persons owing to her affliction, and with the promise of return of a more normal physical existence there went hand-in-hand the belief that this would lead to a fuller life. This in itself removed some of the unnecessarily constricting factors. In a letter prior to her admission to the hospital she had written: "I am getting to the point where I cannot keep a position any length of time. Why is it that we who suffer from this dreadful disease should be spurned by all?" Several months after the operation, despite the occurrence of one attack, she wrote to her physician: "I am feeling 100% better . . . the improvement is remarkable, and I wish to thank you again for all you have done for me."

CASE 2.—The patient was a man aged 22.

A small meningocerebral cicatrix, lying between two gyri in the left frontal region, was removed by Dr. Penfield. At the time when the postoperative Rorschach record was taken the report on the electroencephalogram read: "Complete absence of epileptic activity from the left frontal lobe, where it was found almost continuously before operation, suggesting successful removal of an epileptogenic lesion from this vicinity." Although this patient was cooperative during both test periods, he was reported by the nurses as having been upset by his performance in the first test (fig. 2*A*). He was much more social and approachable during the second test (fig. 2*B*) and showed considerable interest in the outcome of the tests.

A comparison of the two records will show a marked increase in output and evidence of expansion of personality in the second record. The greater output, however, had not affected the good intellectual control, as seen in the percentage

of *F* plus responses, and there was considerably greater ability to respond to emotional stimuli. The sharp rise in the *d* together with the *m* and *K* responses indicates inner anxiety and unrest, not to be found in the more simplified and constricted preoperative record. This patient, a law student, had, it would seem, sufficient insight to be capable of anxiety concerning the possible effect of such an operation. Despite this factor, however, the second record is a fuller one than the first, and, while there is no question that there is a change, it also may well be considered one for the better.

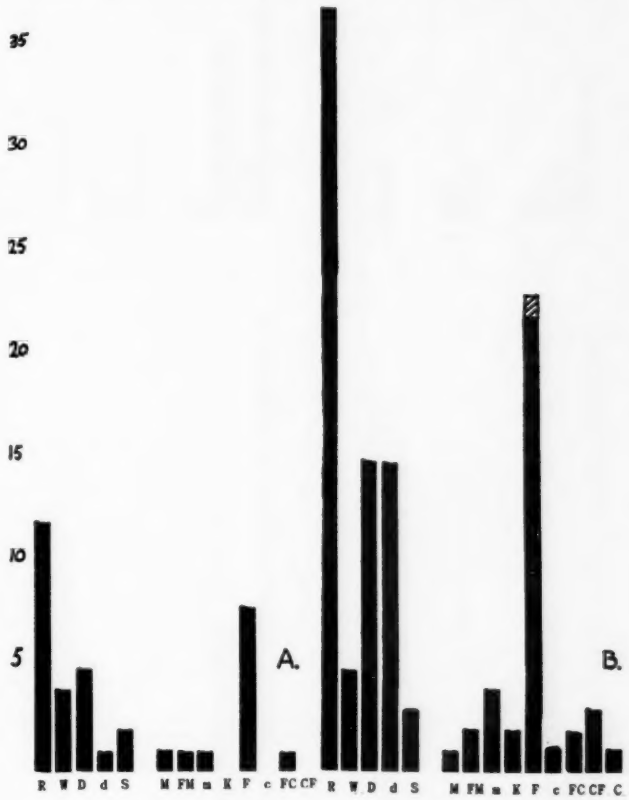

Fig. 2.—Preoperative (*A*) and postoperative (*B*) records in case 2.

CASE 3.—The patient was a man aged 27.

A meningocerebral cicatrix was removed from the left frontal pole. The patient had had a fracture across both frontal lobes, and there was some question of involvement of the right frontal lobe as well, but this was not touched at operation. Before operation the patient was difficult and unsociable. When the second record (fig. 3 *B*) was taken he was appreciably more friendly.

This case also illustrates a postoperative expansion of personality. The relatively high *M* score of the first record, with the lack of all color responses, indicates clearly the introvert personality withdrawn into itself and without a much needed means of approaching the outside world. In the second record this exaggerated

introversion is somewhat offset by the appearance of an *FC* and a *CF* response, but the essential introvert trend is unchanged. This second record must, like those in the 2 previous cases, be considered as showing a change for the better.

CASE 4.—The patient was a woman aged 23.

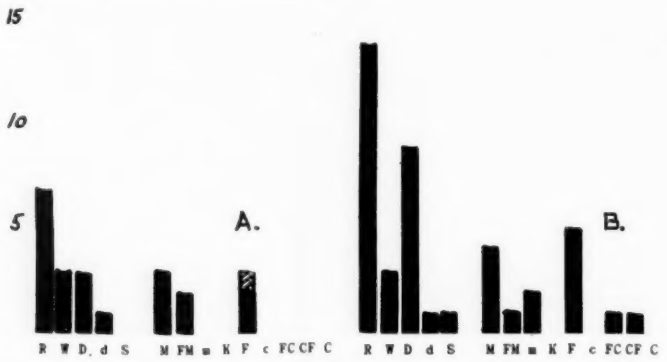

Fig. 3.—Preoperative (*A*) and postoperative (*B*) records in case 3.

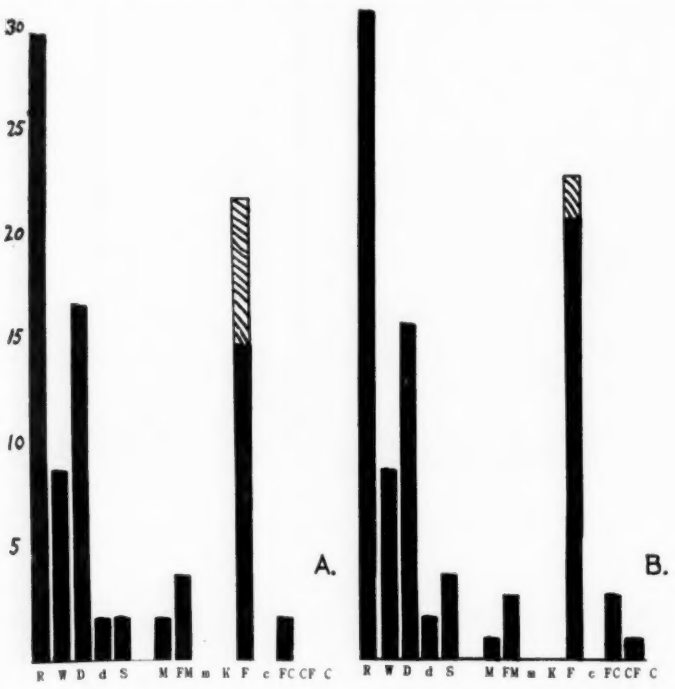

Fig. 4.—Preoperative (*A*) and postoperative (*B*) records in case 4.

Two small gyri, just anterior to the precentral gyrus, largely in area 8, were excised to a depth of 1 to 2 cm. by Dr. Penfield. Craniotomy and a "negative exploration" had been performed a year previously. During both the preoperative and the postoperative testing the patient was extremely cooperative and friendly.

In this case the postoperative record must again be considered changed and slightly improved over the preoperative one, chiefly in the decrease of the *F* minus responses. The case illustrates a point which has been brought out by Oberholzer,[3] namely, that frequent unjustified anatomic responses are characteristic of certain persons with jacksonian epilepsy. In the first record this patient was much preoccupied with anatomic answers, with the result that such answers were below her general standard of accuracy. For example, she gave as her response to card 10: "Lungs, windpipe, breasts, hips and the lower regions and all that." Postoperatively this was replaced by analysis of the parts of the card into much more accurately perceived forms: a butterfly, a horseshoe, a turtle, an octopus and flowers.

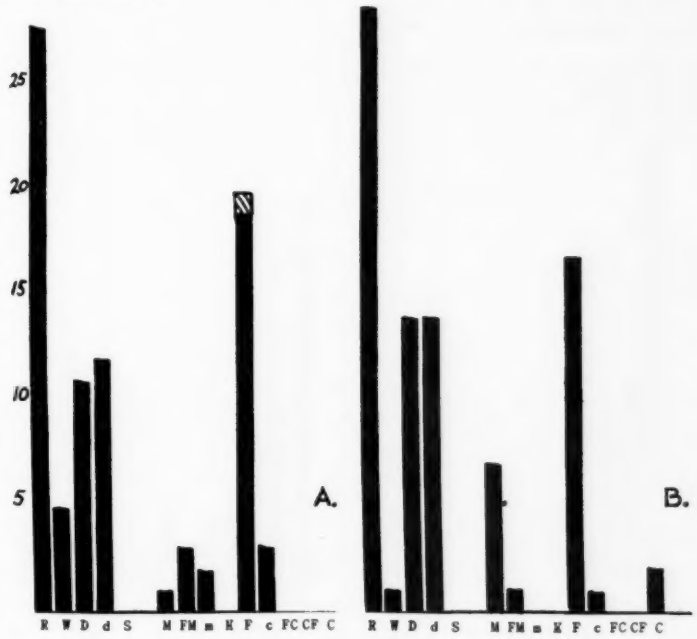

Fig. 5.—Preoperative (*A*) and postoperative (*B*) records in case 5.

CASE 5.—The patient, a man aged 27, had focal cortical seizures. A cicatrix was removed from the left temporal lobe by Dr. Penfield. During the taking of the first record the patient was "peculiar" in his manner, suffered from intense headache and was difficult to deal with. When given his second test he was much more expansive and friendly; he was at that time free from pain, after a long postoperative course in which he had been markedly aphasic.

The individual abnormalities of the two records in this case are not apparent by this means of presentation. The *d* responses were, in fact, replaced by the *dr* or *dd* type. As was explained in part I, however, in order to simplify the psychogram certain symbols were omitted, including *dd* and *dr*. These responses, which

3. Oberholzer, E.: Rorschach's Experiment in Traumatic Mental Disorders, read at the annual meeting of the American Psychiatric Association, Chicago, May 8-11, 1939.

are concerned with very small areas of the cards (*dd*) and rarely utilized areas (*dr*), indicate a bizarre mental approach (except when the general constellation indicates an exceptionally gifted person). The forms seen in these two records were of such a kind that, while difficult to classify as *F* minus, they were yet descriptions rather than interpretations. The whole record, in fact, is similar to those described by Oberholzer [3] as belonging to "traumatic dementia" (traumatic psychosis?). Interestingly, later there was some question of institutionalizing this patient, and the presence of psychotic traits was considered seriously by several clinicians. One would be inclined to regard the second record as better in the rise of *M* from 1 to 7 and in the appearance of some color responses, albeit only of the pure *C* type. However, the *W* responses drop, making for an even greater preoccupation with the *d* answers. In this case the second record shows change, with somewhat doubtful improvement.

In cases 6 to 10 there was no improvement and virtually no change in the second record.

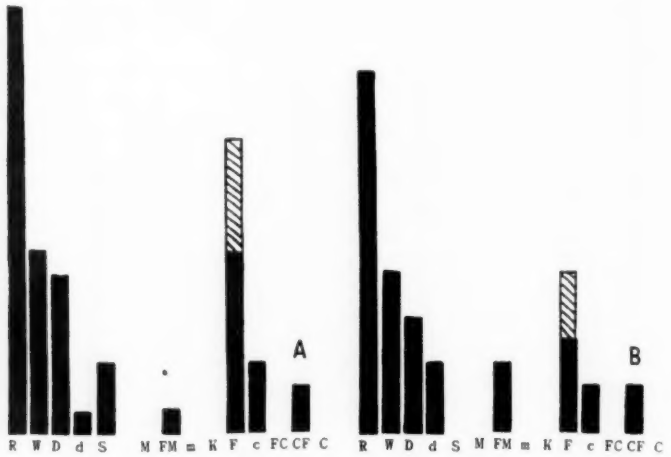

Fig. 6.—Preoperative (*A*) and postoperative (*B*) records in case 6.

CASE 6.—On this patient, a man aged 21, right parieto-occipital craniotomy and removal of a meningocerebral cicatrix and focal area of microgyria were performed by Dr. Penfield. Two years previously the patient had had a similar scar removed. He had been free from attacks for two years prior to their recurrence at the time of the second operation. The patient was somewhat antagonistic during both tests. He had had one seizure three days after operation.

The preoperative record in this case deviated from the normal in the lack of all *M* and *FC* responses and in a too high percentage of *F* minus responses. These obvious defects were not rectified in the postoperative record. Neither record gave a particularly encouraging picture.

CASE 7.—In a youth aged 16 there was removed an area of cortex 1 by 5 cm., with whitened arachnoid, located between the first and the second temporal convolution. The operative comment was: "This comes nearer being a negative exploration than a satisfactory removal." The patient was cooperative during both tests.

The record in this case contains *M* minus responses, which are never obtained from normal persons and, according to Oberholzer, are characteristic of jacksonian epilepsy. The *M* minus responses are present in the second record also. The only other point of interest is the rise in *c* in the postoperative record. The possible significance of this will be discussed in the section on patients who had "negative explorations."

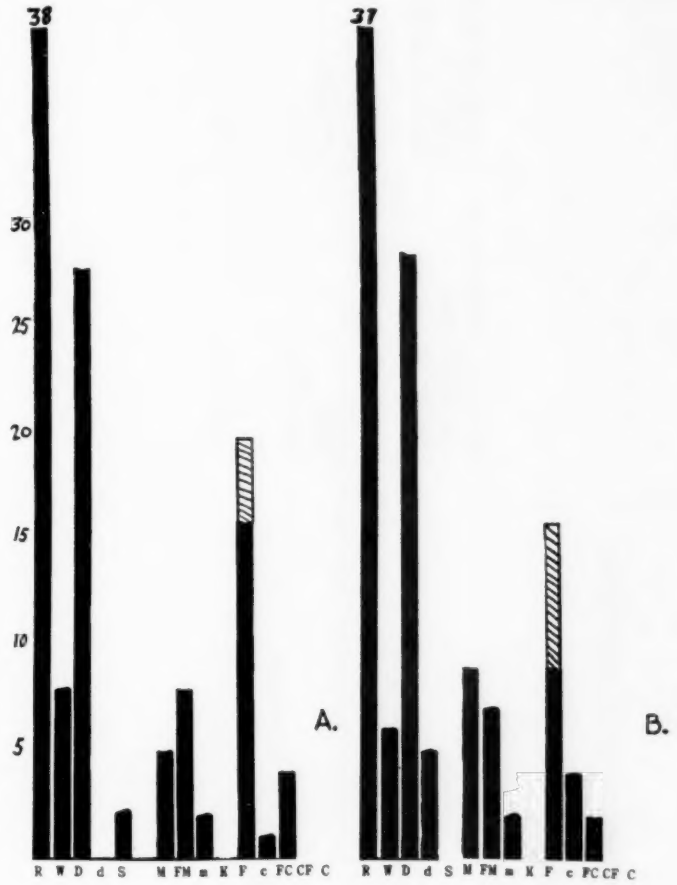

Fig. 7.—Preoperative (*A*) and postoperative (*B*) records in case 7.

CASE 8.—A boy aged 15 underwent extensive removal of a meningocerebral cicatrix in the right frontoparietal region (chiefly the postcentral face, throat and tongue areas). The patient was cooperative in both examinations.

The obvious lack of all emotional adjustment indicated in the record is similar to that in case 3. In contrast to case 3, however, there was no return to a more normal picture postoperatively. This overemphasized introversive picture may, I suggest, be typical for certain types of persons who retreat into themselves as a refuge from the social difficulties inherent in the situation of epileptic attacks.

CASE 9.—A man aged 23 underwent removal of an area of softened brain from the right temporal lobe just below the rolandic cortex. He was cooperative at both examinations.

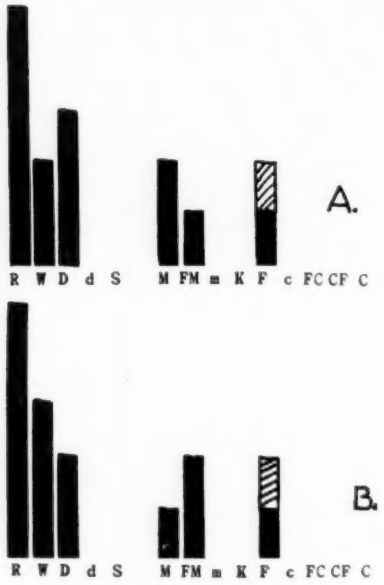

Fig. 8.—Preoperative (*A*) and postoperative (*B*) records in case 8.

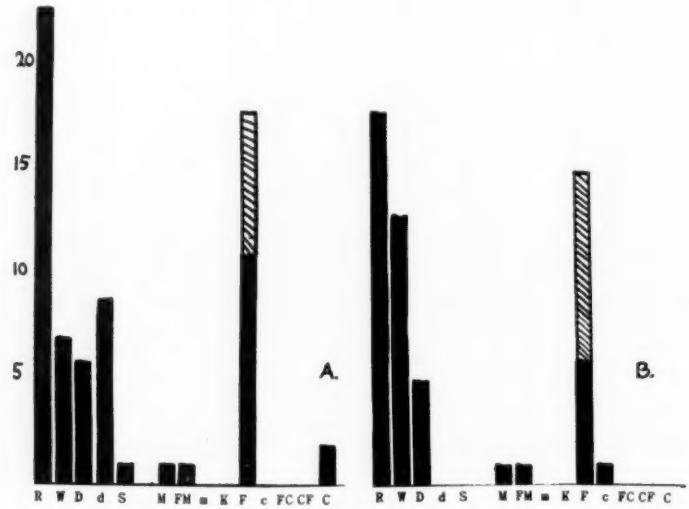

Fig. 9.—Preoperative (*A*) and postoperative (*B*) records in case 9.

That these records are not those of a well balanced normal person can be seen from comparison with figure 2, part I. The percentage of *F* minus responses is too high, and the *F* : *R* ratio is too heavily weighted in terms of *F*. There are no indications of normal emotional responsiveness. It should be noted that, if any-

thing, the postoperative record is less good than the preoperative one, in that the rise of *F* minus responses in this case illustrates an increase in poor, unjustified anatomic responses, of the kind which dropped out in the second record in case 4.

CASE 10.—A man aged 26 presented "diffuse scarring of the frontal lobe over an area involving most of the lateral aspect of the frontal lobe. Removal of tissue of considerable extent, down as far as the white matter, was carried out. The postoperative course was stormy, involving reopening the skull and removal

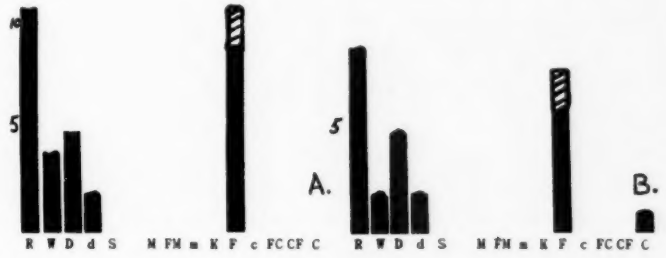

Fig. 10.—Preoperative (*A*) and postoperative (*B*) records in case 10.

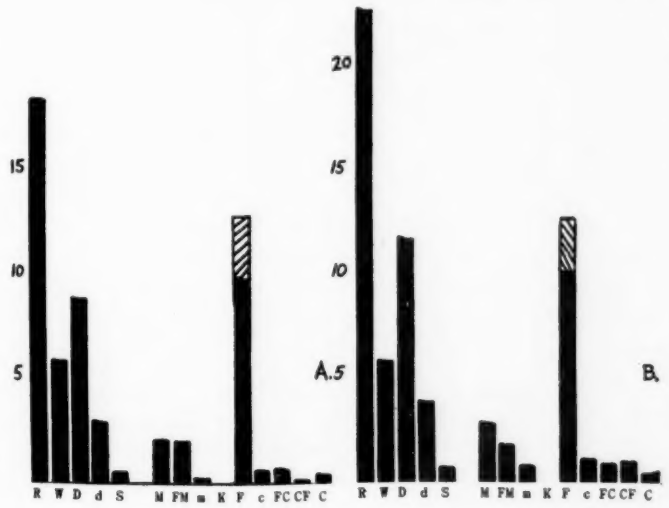

Fig. 11.—*A*, composite preoperative record in 10 cases of focal epilepsy. *B*, composite record in 10 cases of focal epilepsy six weeks after operation.

of a hematoma" (from the case history and Dr. Penfield's operative notes). This patient was aggressive and impatient during the postoperative Rorschach examination.

The records in this case were the most abnormal of the group and the only ones which were virtually identical with those associated with cerebral damage produced by tumor (fig. 7, part I). This is particularly interesting in view of the extent of cerebral damage mentioned in the history.

Summary.—In 5 of the 10 cases in group A there was a change in the postoperative record which was indicative of an improved psychologic condition. In the remaining 5 cases there was virtually no change, although the second record in case 9 is probably indicative of a less good mental condition than the first.

Although, with the exception of that in case 10, none of these records showed the uniform abnormality of the records of patients with tumor described in part I, they all indicate to a greater or lesser degree a deviation from an essentially well balanced, normal personality. However, these deviations are of markedly individual kinds, representing different personalities coping with difficulties with greater or lesser ability.

These 10 cases having been described in detail, consideration may now be given to the composite picture afforded by their preoperative and postoperative pictures. It will be seen that there are a slight increase on the affective side of the graph postoperatively and a rise in the *M* responses, but that otherwise these psychograms do not differ one from the other, nor can they be considered as showing any striking deviation from the normal composite picture of figure 2, part I. The conclusions which may be drawn from these 10 cases will be reserved until all the psychograms have been presented.

GROUP B: *Patients Studied Postoperatively and After a Year's Interval.*—The main interest in the 4 patients was in how the records corresponded with reports from independent sources concerning the patients' adjustment and behavior during the interval between the two tests. One is dealing with a variety of environments and with a much greater interval than in the case of group A. Moreover, the stresses imposed by readjustment to normal life were much greater than those imposed by the first six weeks of convalescence in a comparatively sheltered environment.

CASE 11.—A man aged 26 underwent removal of the left frontal pole in 1934, after seizures. There was a previous history of abscess of the brain. Rorschach records were taken in 1938 and in 1939. One convulsion occurred in February 1939, that is, between the taking of the two Rorschach records. None had occurred postoperatively prior to that date.

The two records are of particular interest when compared with each other and when contrasted with the restricted responses of patients with tumors of the frontal lobe. Figure 12*A*, although it shows the patient to have been normal in mental approach and above the average in intellectual capacity, reflects possible difficulties for him due to the absence of all responses on the affective side of the graph. A startling change, however, is observable in figure 12*B*, indicating that the patient at the time of the test was laboring under a great strain of anxiety. It might almost be considered the record of a person with an anxiety neurosis. The *m*, *c* and *d* responses, which indicate intense inner unrest and anxiety, are out of all proportion to the others. This Rorschach picture, taken without any knowledge of the patient's circumstances at the time, was confirmed clinically some months later, when the physician stated that "he might have been

considered to have had an anxiety neurosis at that time, so great was the psychologic disturbance." Acute personal difficulties and the occurrence of an attack, the first since 1934, had affected him profoundly. The important point to notice is that this sensitive and complicated personality picture is entirely different from the over-simplified, constricted and restricted personality picture which has characterized both the presence of a tumor or neoplasm in the frontal lobe and the state shortly after incomplete removal of a tumor. The postoperative record of this patient is

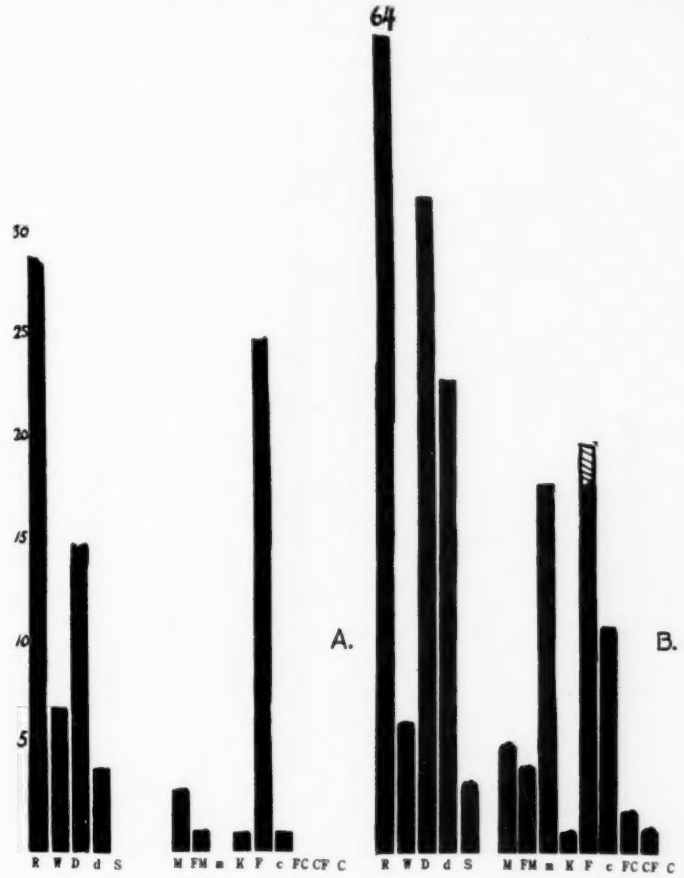

Fig. 12.—*A*, record taken in 1938 in case 11. *B*, record taken in 1939.

certainly not normal, but its abnormality is of the kind which is found in persons who have no cerebral lesions. In other words, removal of the left frontal pole did not in this case produce a typical "organic picture" in the Rorschach record. The patient's realization of difficulties inherent in his physical condition, together with other pressing personal difficulties, is registered in his basic personality pattern. Physical and psychologic factors combine to give, in this case, not a restricted, insensitive personality but one suffering from the effects of exposure to acute psychologic strain. This case seems to be an example of what Oberholzer [3] has described: "After traumatic injury, when cure begins to take place, the residual effects of neurotic manifestations appear alongside more normal findings."

Case 12.—A man aged 27 underwent bilateral removal of a meningocerebral cicatrix from the frontal region, by Dr. Penfield.

This case is one of particular interest because of the comparison which is possible between this patient, K. M., and Brickner's Mr. A.,[4] on whom a similar operation was performed, in the field of psychometrics and in the Rorschach test.

In an article devoted to a detailed consideration of this patient, Hebb and Penfield[5] have described the results of a study of his clinical behavior and his postoperative mental capacity by means of a battery of fifteen psychometric tests, two of which were also given preoperatively. The change in behavior as noted by these authors was exceedingly marked. Before operation, they described the patient as "a behavior problem, irresponsible and childishly stubborn." Fifteen

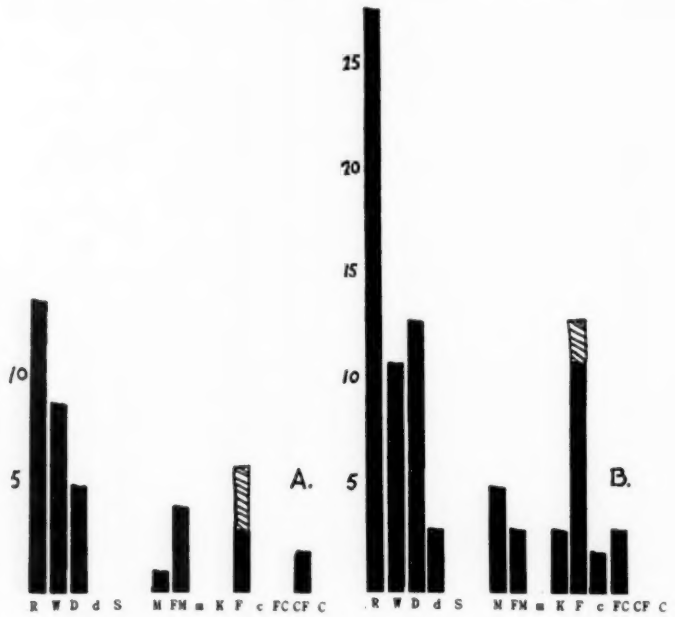

Fig. 13.—*A*, record taken forty days after the operation in case 12. *B*, record taken fifteen months after the operation.

months after the operation his normality and the stability of his general demeanor were apparent to all. This change in general demeanor is epitomized in a letter to Dr. Hebb from the patient's brother: "His memory seems to be good, and he is more steady in his ways, and does not act childish, as he did prior to the operation. His father and mother both think K. is 100 per cent better."

While this change in behavior is dramatic and in marked contrast to the postoperative behavior of Mr. A., the psychometric results do not give such a

4. Klopfer, B., and Tallman, G.: (*a*) Rorschach Study of a Bilateral Lobectomy Case, Rorschach Research Exchange **1**:31-36, 1937; (*b*) A Further Rorschach Study of Mr. A., ibid. **3**:77-88, 1938.

5. Hebb, D. O., and Penfield, W.: Human Behaviour After Large Bilateral Removal from the Frontal Lobes, Arch. Neurol. & Psychiat., to be published.

clear picture of a change. While the battery of performance and intelligence tests used by Hebb and Penfield showed that postoperatively K. M. fell within the normal range, the comparison of preoperative and postoperative psychometric performance rested on his scores in the Binet and the Beta tests alone. With the Binet test the preoperative intelligence quotient (on form L) was 83 and the postoperative score 94 (a difference which when the probable error and the practice effect due to three intervening uses of forms L and M are considered is not marked). Moreover, the intelligence quotient of Mr. A., despite his abnormal behavior, was also 94 when measured in 1938.[4b]

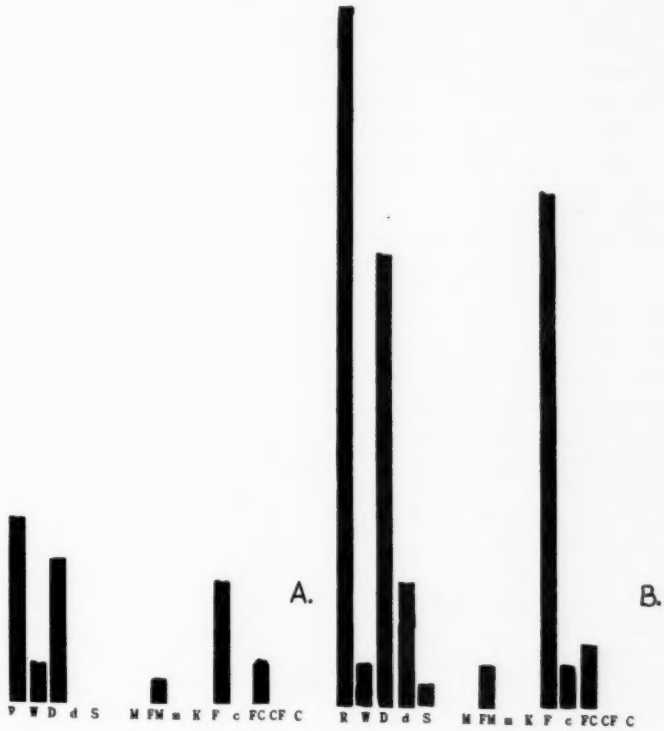

Fig. 14.—*A*, record taken six weeks after the operation in case 13. *B*, record taken nine months after the operation in the same case.

Since the psychometric tests did not mirror the extent of the change in behavior as indicated clinically, it seemed of particular interest to take Rorschach records of this patient. Unfortunately, no preoperative record was taken from either this patient or Mr. A. My first Rorschach study of this patient was made forty days after operation (fig. 13*A*), the second, fifteen months after operation (fig. 13*B*). There is some question of how to characterize the patient's behavior as observed clinically during the period prior to taking the first record and on the actual day of examination. Immediately after operation he was disoriented and seriously disturbed mentally. Subsequent to this he was characterized as "facetious and vulgar," and some evidence of instability was noted by the nurses as late as the fortieth day after the operation.[5] It seems safe to assume, therefore, that the first Rorschach

record represents a period when the patient was still not an essentially normal person, even if his abnormality was somewhat different from that which characterized him preoperatively.

The first record, indicating as it does the poor control (high percentage of *F* minus responses), the less adjusted emotional responses (*CF*) and the dominance of the primitive urges (*FM* greater than *M*), reflects an infantile and irresponsible personality. He was, in Dr. Klopfer's words, "a person without common sense, 'direction' or maturity." The second record, however, shows a remarkable readjustment. The previous defects are neutralized to an amazing degree. The *M:FM* ratio is reversed; *FC* responses have replaced the *CF* type. A much needed sensitivity to others and a knowledge of himself are now represented. The percentage of *F* minus responses has decreased to the normal proportions. To quote again from Klopfer's analysis: "A widening of the mental approach, a sharpening of logical functioning . . . an increased flexibility and a return to the resources of inner life . . . a return of emotional adjustment."

Since the three Rorschach records of Mr. A., taken by Tallman and interpreted by Klopfer, show no such marked improvement in mental capacity or in personal adjustment, but indicate rather progressive mental deterioration, this strikingly improved record of K. M., taken fifteen months after the operation, seems another proof of the fact brought out by Hebb and Penfield[5] that removal of cerebral tissue in itself is not sufficient to account for the particular characteristics of Mr. A's blatant and uncontrolled postoperative behavior.

CASE 13.—A girl aged 13, after one year of seizures, underwent a left parietal osteoplastic craniotomy, which was performed by Dr. Penfield. Focal microgyria, with some meningocerebral adhesions, was observed. This area was completely excised. The postoperative course was uneventful and, owing to the absence of epileptogenic waves, all medication was withdrawn.

The Rorschach test was given first a few weeks after operation and subsequently nine months later. The second record shows improvement and expansion of personality over the first. An interesting parallel to this was found in the report given spontaneously by the patient's married sister: "Since operation there has been a great change for the better; she used to be depressed, bad tempered and naughty, but now she is always good humored, works without being urged and is well able to organize her life."

Since the second record contains no startling change in the type of personality structure and since the first record itself contains no marked abnormalities, one must assume that during the year of seizures prior to operation the child had been cramped by some inhibiting factor so that she could not function at her best and that she was in consequence maladjusted, but that no warping of the personality had taken place during that one year. The fact that the improvement in personality occurred so soon after operation bears this out.

CASE 14.—A boy aged 16 underwent the removal of the left frontal lobe, following abscesses of the brain, by Dr. W. V. Cone.

That the occurrence of a convulsive seizure some time after operation need not cause a psychologic catastrophe for the patient (as occurred in case 11) is seen in the records of this boy. Figure 15 *A*, taken a few months after operation, shows a fairly normal picture. Figure 15 *B*, taken a year later (a few days after a series of attacks), indicates distinct loss of intellectual control and of the emotional responses, but there is no question of anxiety or psychologic unrest. During the year this boy had returned to school and was intellectually and socially normal.

Whether the sharp increase in poor form answers was transient, due to the immediate effects of the convulsions, or whether there will be a permanent decrease in intellectual ability is too soon to answer. The second record, however, unlike those in cases 12 an 13, is obviously less good than the first.

Summary.—In summarizing these four records it may be said: A marked improvement in the Rorschach record can be seen in cases 12 and 13. During periods of nine and fifteen months, respectively, the record changed from an inadequate to a much fuller one (case 13) and from one showing abnormality to one manifesting better adjustment (case 12). These improvements are paralleled by the reports from the patients' homes. In case 11 there was an interesting change in the record. Four years after the operation, at the time when the first

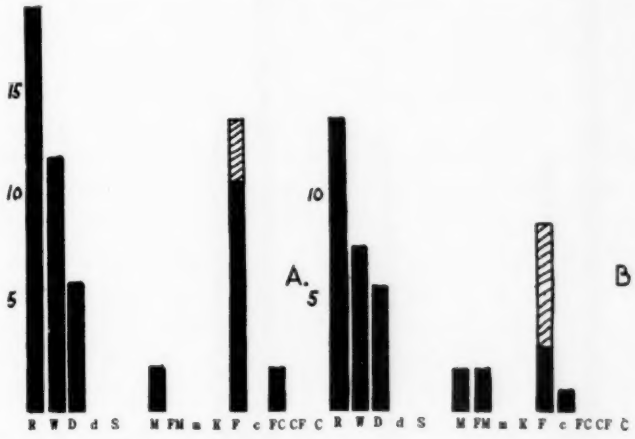

Fig. 15.—*A*, record taken a few months after the operation in case 14. *B*, record taken a year later (a few days after a series of attacks).

Rorschach record was taken, the patient gave the record of an intelligent person, though one lacking in the ability to make a real social and affective adjustment. One year later, however, the record showed great anxiety. It is suggested that the recurrence of a convulsion, in the light of the patient's medical knowledge, and the acute psychologic difficulties at that time are clearly reflected in this patient's record. The first record in case 14, taken a few months after the operation, is a relatively good one; the second, concomitant with a series of attacks, shows some decrease in intellectual capacity.

GROUP C: *Patients Examined Once Postoperatively.*—In addition to these 14 patients, 10 others were examined by the Rorschach method (postoperatively only). Since no strikingly new facts came to light from these patients, I have not included their psychograms here. It suffices to say that a variety of personality types emerged, as in the

cases already considered. The composite picture in no way differed from that in figure 11. In 2 cases the records approximated the psychograms seen in cases of cerebral tumor, illustrated in this section by case 10 (fig. 10). This seems to be correlated in each case with an extensive pathologic alteration of the cortex. In 1 case there was neurotic anxiety.

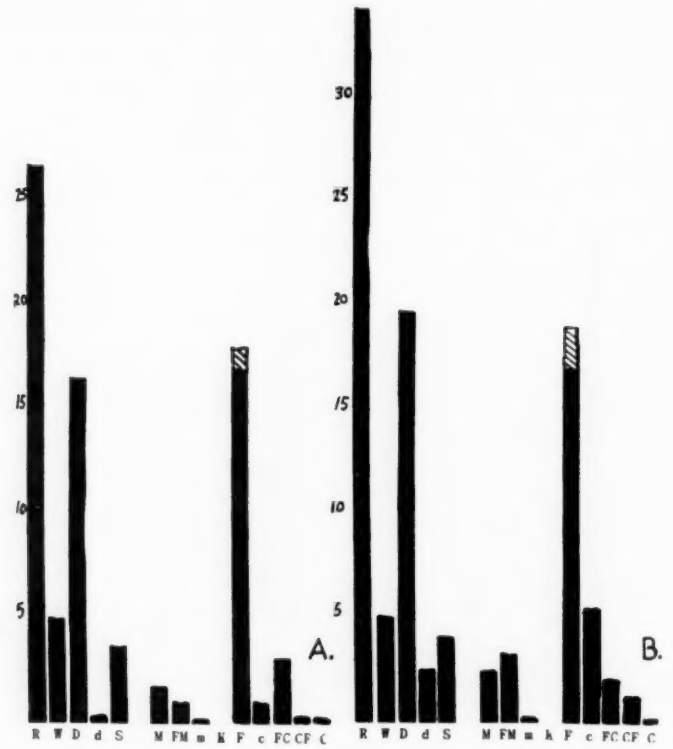

Fig. 16.—Composite picture of 4 cases in which "negative exploration" was carried out. *A*, preoperative record; *B*, postoperative record.

CRANIOTOMIES AND "NEGATIVE EXPLORATIONS"

I shall consider here for the effect of operation a small group of important control subjects, namely, persons with focal epilepsy on whom a "negative exploration" was performed, i. e., a craniotomy which revealed no pathologic alteration amenable to surgical excision. The composite preoperative and postoperative pictures of these 4 patients should be compared with the various composite pictures in this and in the previous study. It will be seen that the records of these patients in no way fit in with those of the group with gross damage from cerebral lesions. There is, however, one interesting characteristic

shown in the composite postoperative picture (and in each of the 4 individual postoperative records), namely, a sharp rise in *c* responses, which one may assume is an indication of increased sensitivity, or even of apprehension. The rise in the composite picture is from 1 to 5, as large a change as one finds anywhere; moreover, this is derived from every one of the individual records and is not imposed on the group by an excessive score in 1 case only.

One is tempted to mention here Goldstein's suggestion that the less seriously damaged organism is the more apprehensive or the more concerned with its own disability. In the 18 records of patients from whom cerebral tumors were removed one finds only slight indication of this increased sensitivity in 3 cases.

It seems particularly important in view of such a finding to do all one can to determine more exactly what particular character trait actually corresponds to the introduction of some new mode of perception—in this case to the sudden addition of the *c* scores in the record. Since it is not always possible to draw such information from the patients themselves, if indeed they are actually aware of it, it is interesting to note the following comment made by the parents of a patient whose only postoperative change, as far as the Rorschach test was concerned, was an increase in the *c* score. "He has very little resistance or nerve to bear pain or hurt. As you may know, he has to have 'hypo' injections all the time, and at times the dread of them seems more than he can stand. He used to go quite bravely to the dentist before his operation to have a tooth pulled, all alone, but now the very thought of it makes him shudder." A similar report in the case history of this patient, made by the nurse, stated: "He cried loudly for some time, saying he was afraid to have blood taken, that it would hurt. He did not respond to reasoning and refused to be comforted. This appears to be in sharp contrast to his serene and almost stoical preoperative behavior." It seems that the uniform addition in these cases of a new mode of response in the Rorschach test may be indicative of a real psychologic change induced by the purely psychologic aspects and effects of the experience of the operation.

EFFECT OF MEDICATION ON RORSCHACH RECORDS

Patients coming to the Neurological Institute have almost invariably been receiving some medicament (usually phenobarbital) over a period of time. When during their stay in the hospital medication has been stopped for any reason, I have attempted to take a Rorschach record for the sake of comparison. All the records considered so far, however

(with the exception of case 6, postoperative record, and case 13, record *B*), have been taken while the patients were obtaining their usual doses of the prescribed sedatives.

Certain cases, however, were specially studied from this point of view, and some indication of the results is given here.

Cases 15 and 16 were those of 2 patients with cryptogenic epilepsy from the outpatient clinic who were described as somewhat deteriorated. Both had been given medication for years, but this was discontinued for a period in order that electroencephalograms might be made. It will be seen that the records of these patients are remarkably similar.

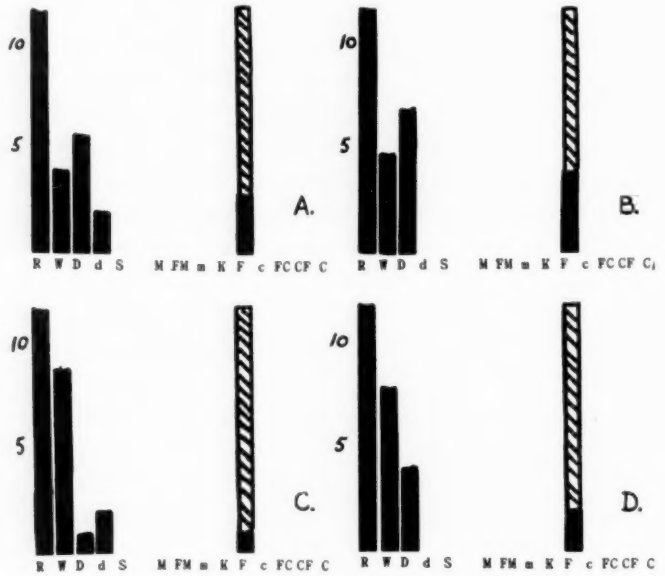

Fig. 17.—*A*, record of the patient in case 15 while receiving medication. *B*, record of the same patient without medication. *C* and *D*, similar records of the patient in case 16.

Moreover, they are quite distinct from those of the patients with tumor and from those of the nondeteriorated patients with focal epilepsy, which have just been considered. There would also seem to be no effect on the record after the cessation of medication. However, it will be noticed that the patient in case 17, who was far from deteriorated and who gave high scores on performance and intelligence tests, made a far better record when the medication was discontinued.

As will be brought out in the comment, one cannot help feeling that a record which still shows some *M* and color responses, though

made under handicaps, psychologic or physical, has a better chance of improvement with the removal of these handicaps than one without indications of psychologic potentialities. One would therefore expect the cessation of medication to give rise to a better record in case 17, but not in case 15 or case 16, and this is confirmed by the results.

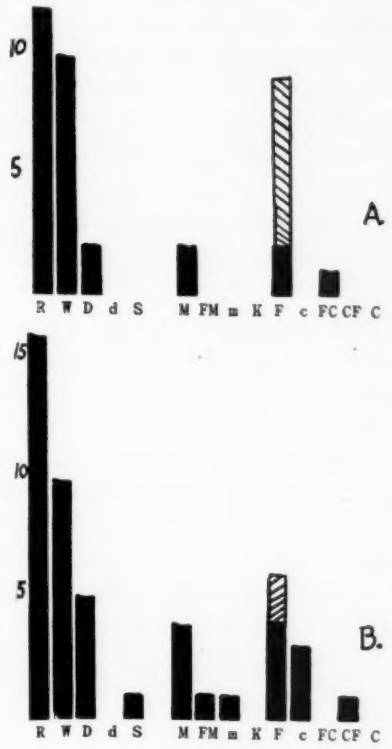

Fig. 18.—*A*, record of the patient in case 17 while receiving medication. *B*, record of the same patient while receiving no medication.

COMMENT

Thus far, consideration of the psychograms of patients with focal epilepsy allows one to draw the following conclusions with regard to the original questions.

1. It is obvious that the restriction and constriction shown in the records of patients with cerebral tumor are not characteristic of all types of cerebral lesions. Of the 10 patients with focal epilepsy, studied preoperatively and postoperatively, the records of only 1 (case 10) showed a similarity to this Rorschach picture.

2. After removal of varying amounts of tissue from various areas for these discrete and noninfiltrating lesions, the majority of postopera-

tive records showed a variety and individuality not found in the postoperative records of the group with tumor. In group A, 5 records showed definite improvement over the preoperative ones, 4 remained virtually unchanged and 1 record was considered to be less good. Only 1 postoperative record (again in case 10) approximated the picture characteristic of tumor, and this patient was known to have an extensive lesion. In group B, after one year's interval, 2 records showed marked improvement, and a third illustrated in its change the onset of an acute phase of anxiety and stress. A fourth showed some decline in intellectual control, which was paralleled by the onset of attacks. The 10 additional cases, which were not illustrated here, lead to the same general conclusion, namely, that there is no typical Rorschach record for patients with focal epilepsy. An approximation of the tumor psychogram appears to be correlated with topographically extensive or diffuse cerebral damage.

3. This of necessity leads me to answer my third question in the negative. The patients studied here do not exhibit such characteristics that the term "epileptic personality," or indeed any other uniform type of personality, can be attributed to them. This does not mean, however, that the records of these patients are those of well adjusted normal persons; the preoperative records in particular reveal varying degrees of deviation from the normal picture (fig. 2, part I).

So much for the general questions raised at the start; one is in a position now to go several steps further. For example, in the 10 cases studied in group A, in which one found that 5 of the postoperative records were changed for the better, can one discover characteristics of the records which will enable one to postulate why such an improvement took place? Or, rather, do the first records of these patients indicate whether or not one could expect improvement, given the removal of some physically handicapping factor and the accompanying psychologic release?

There are certain standard requirements in a good Rorschach record, of which one may consider five as to their prognostic value here. One might say that a record should contain (1) some *M* response; (2) some *FC* or *CF* response; (3) an adequate mental approach (proper distribution of *W*, *D d* and *S* responses); (4) a high percentage of F plus responses, and (5) some variety of content (i. e., two spheres of interest over and above the animal and human).

One may make the hypothesis, then, that when the preoperative record shows all or several of these, despite a restricted output or other less encouraging signs, the chances for improvement are good.

Are such criteria valid when compared with the results? The accompanying tabulation shows the presence or absence of these criteria in the respective preoperative records. The cases are listed in the order in which improvement of the second record seemed the most striking. It would seem that use of such criteria "works" surprisingly well: The only case in which improvement was noticed in the second record which did not seem to be warranted by this method of prognosis is case 3.[6] Beyond this, one can say that the more of these signs the preoperative record showed the greater the postoperative improvement. The cases in which there was no improvement were those in which not more than two of these criteria were present in the preoperative record.

Cases in which the second record was considered improved	1	2	3	4	5	Total No. of Criteria Present
1	*	*	*	*	*	5
2	*	*	*	*	*	5
3	*			*		2
4	*	*		*	*	4
5	*		*		*	3
Cases in which the second record was not improved						
6		*			*	2
7	*	*				2
8	*					1
9	*					1
10				*		1

If the validity of such criteria should be further verified, they might prove of value in selecting the patients most likely to benefit in their general condition by operative intervention. In view of this it will be seen why I considered the record of case 17 more likely to be improved when the patient was without medication and why I did not expect improvement in cases 15 and 16.

The results must now be discussed briefly in relation to those of Oberholzer,[3] Stauder [2] and Guirdham,[7] whose studies have done much to extend knowledge beyond Rorschach's original observations, made on a relatively small number of epileptic patients.

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6. Possibly further study will reveal the necessity for considering some of these factors as more important for, or better indicators of, future improvement than others. For example, the appearance of more than 1 *M* response in a preoperative record might receive more weight.

7. Guirdham, A.: The Rorschach Test in Epileptics, J. Ment. Sc. **81**:870-893, 1935.

Since none of the patients in these studies had undergone operation for removal of an epileptogenic focus, my group of patients with focal epilepsy are not comparable with them. Moreover, none of my patients were psychotic. The patients studied by Guirdham included 100 in whom epilepsy was associated with mental defect, mental disease and epileptic dementia. Stauder's series included many patients with "genuine" epilepsy accompanied by "serious clinical personality changes." Oberholzer referred chiefly either to patients whose clinical condition was "traumatic psychosis" or to those who showed other clinical signs of altered personality.

This is important to remember when comparing their results with mine. For example, perseveration of a single Rorschach response, found as the most striking characteristic by both Stauder and Guirdham and mentioned by Rorschach [8] and Oberholzer,[3] was not observed in this series of patients but was prevalent in the cases of widespread cerebral damage following removal of cerebral tumors and before operation in such cases, particularly when increased intracranial pressure was present.[9] I have observed patients with perseveration of as much as 100 per cent (deteriorated patients with cryptogenic epilepsy, discussed on page 1083). However, these patients differed clinically from those in groups A and B, discussed on page . . . .

It is interesting to note that Guirdham,[7] although he found several characteristics in which the epileptic patient differs from the normal person, concluded that for the group as a whole there was no constant Rorschach reaction type. Stauder,[2] on the other hand, found his Rorschach picture of the patient with "genuine" epilepsy so inseparable from that condition that he concluded it to be an indication of the epileptic constitution. I did not find that this particular group of patients with focal epilepsy showed any indication of such uniformity or epileptic constitution. In short, while I have observed records similar to those described by Stauder among deteriorated patients with cryptogenic epilepsy, such records were not observed among the patients with focal epilepsy in my groups.

All Rorschach records stand in need of verification from the clinical facts. If, for example, one makes a "blind diagnosis" of great anxiety and apprehension in the case of a given person, the obvious need is to correlate this with what is known about the person from all other

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8. Rorschach, H.: Psychodiagnostik, ed. 2, Berne, Hans Huber, 1932.

9. In recent publications concerning the perception of ambiguous figures (Harrower, M. R.: Changes in Figure-Ground Perception in Patients with Cortical Lesions, Brit. J. Psychol. [Gen. Sect.] **30**:47-51, 1939; Some Factors Determining Figure-Ground Articulation, ibid. **26**:407-424, 1936), I have shown that, in contradistinction to the findings for normal persons, perseveration is a characteristic of the perception of patients with cerebral lesions.

sources. The validity of the Rorschach method has rested on such constant verification. Theoretically, however, to be of most value to a scientific understanding of behavior in the widest sense, all records also need to be "equated" with changes in cerebral structure and function at the time the record is taken. Needless to say, except in rare cases, one cannot "lift the lid" to see the concomitant cerebral phenomena. One reason, therefore, why an exhaustive study of Rorschach records in cases of different types of cerebral abnormality seems so important is that one has, when operation is necessary, two checks on the interpretations instead of only one.

Marinesco, Kreindler and Copelmann,[10] in articles published some years ago, have in their bold hypotheses suggested certain specific cerebral counterparts to specific Rorschach responses. Using pavlovian terms, they suggested that the *W* responses, for example, reflect irradiation of excitation over the visual analyzer, and that *d* responses, on the other hand, are the psychologic counterpart of inhibition of this excitation. *M* responses they saw as the spread of such excitation from the visual to the motor areas. While this study cannot go so far as to substantiate any of their hypotheses, it would seem that one is entitled to assume a direct relation between certain conditions of widespread cortical damage and a typical constricted record, epitomized in the psychograms in part I of this study.

This brings me once more to a consideration of the term "organic personality," with which the present investigation started. Although widespread and diffuse cerebral damage (tumors, increased intracranial pressure and large incomplete removal of tissue) may yield Rorschach records of the restricted type (fig. 7, part I, and fig. 10, this paper), cerebral damage of a more discrete type, such as is seen in many cases of focal epilepsy, need not give such a personality picture. In these cases the Rorschach records may (preoperatively) be of such a type as to suggest that the patient is capable of a wider range of psychologic reactivity but is inhibited by mental and physical factors from functioning adequately.

It is interesting to note that Piotrowski,[11] in a recent article, has shown that the patients most capable of profiting by the insulin treat-

10. Marinesco, G.; Kreindler, A., and Copelmann, L. S.: Essai d'une interprétation physiologique du test psychologique de Rorschach. Son application à l'étude de la dynamique, cérébrale des jumeaux, An. psihol. **1**:14-26, 1934; Le test de Rorschach et le dynamique de l'écorce cérébrale d'après les lois réflexes conditionnels de Pavlov, Ann. med.-psychol. (pt. 1) **93**:614-623, 1935. Copelmann, L. S.: Psihodiagnosticul Rorschach in lumina activitatii dinamice a scoartei cerebrale, Bucarest, Societatea Romana de cercetari psihologice, 1935.

11. Piotrowski, Z.: The Prognostic Possibilities of the Rorschach Method in Insulin Treatment, Psychiatric Quart. **12**:679-689, 1938.

ment of schizophrenia are those in whose pretreatment records some indication of *M* responses and color responses are found. I suggest that these and other signs in the records of patients with focal epilepsy will indicate the persons most likely to benefit by operative intervention. On this assumption, the better psychologic record indicates a nervous system better able to make use of therapeutic and surgical aids for the needs, mental and physical, of the whole organism.

In part I of this study I raised the question why personality changes in patients with cerebral lesions occur and suggested three possible explanations: (*a*) The absence of cerebral tissue is responsible; (*b*) the presence of pathologic tissue is the determining factor, and (*c*) mutually influential physical and psychologic factors must be taken into account.

The first hypothesis is ruled out, it seems to me, by the results in the cases of tumor, and it is further excluded by the results of this study with patients operated on for focal epilepsy and by the findings of Hebb and Penfield in their detailed analysis of the case of K. M. (case 12, this paper). The postoperative records in cases of tumor (part I) were consistently, though slightly, better than the preoperative ones. In this study it has been found that in group A 5 of 10 postoperative records show improvement, 4 remain virtually unchanged and only 1 seems to indicate deterioration. In group B there is definite improvement in the second postoperative record in 2 cases, after longer intervals than were taken into account in group A. The only record which after a year's interval is less good is one taken just subsequent to a series of attacks. In this case one might be led to assume that a direct relation exists between the presence of abnormal cerebral function associated with the epileptic activity and the less good Rorschach record.

However, this is not the whole story, and one is entitled, I think, to consider as the more satisfactory hypothesis that in which both psychologic and physical factors are necessary to explain and account for improvement or lack of it in a patient's Rorschach record. For example, one and the same physical occurrence (a convulsion) may have different psychologic effects on different persons. I suggest, therefore, that, depending on the patient's psychologic makeup before operation, the removal of brain tissue will to a greater or lesser degree aid in producing a better psychologic picture. In other words, the clean removal of an epileptic focus may produce marked improvement in one record but not in another; conversely, the existence of some remaining cerebral lesion, (provided it is not too great) may in some cases produce greater psychologic abnormality than in others, the degree to which it will handicap the subject being to some extent related to the stability or instability of his psychologic makeup. My answer to the question of

the cause of personality changes is therefore in terms of a hypothesis which takes into account mutually interacting neurologic and psychologic factors.

SUMMARY AND CONCLUSIONS

A group of 24 patients with focal epilepsy, all of whom had undergone operation for the removal of nonexpanding atrophic lesions, was studied by the Rorschach method. The patients were studied postoperatively after varying intervals, and 10 were also studied preoperatively to allow a comparison of records obtained before and those obtained after the removal of cerebral abnormalities. A comparison was made of these patients and patients with large infiltrating lesions, as well as of deteriorated patients with cryptogenic epilepsy and of patients on whom craniotomy and "negative exploration" had been carried out.

I believe that no one typical personality emerges in the cases of the patients with focal epilepsy but that there is a wide range of personality difficulties. There was evidence in the records of this group of behavior problems, of neurotic personality and, in 1 case, of possible psychosis. There were markedly introvert and extrovert personalities and all varieties of mental approach. There were 3 cases in which Rorschach signs peculiar to jacksonian (focal) epilepsy appeared, and 3 in which the records approximated the type of personality already described in the paper on cerebral tumors.

With respect to the difference between preoperative and postoperative Rorschach records, I have isolated certain components of the preoperative records which seemed to indicate future psychologic improvement if more favorable conditions could be given the patient. This makes one hope that such studies may make a contribution to prognosis, for if improved psychologic capacity, as evidenced by the Rorschach test, is in itself an index of improved cerebral function, as is suggested by this study, this method may become a prognostic procedure for the selection of those patients who are most likely to be benefited, both mentally and physically, by operative intervention. While it is not possible to make such a claim from this study alone, it is hoped that the hypothesis may prove of value for the basis of future work.

NEUROHISTOPATHOLOGIC CHANGES WITH METRAZOL AND INSULIN SHOCK THERAPY

AN EXPERIMENTAL STUDY ON THE CAT

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AND
MATTHEW T. MOORE, M.D.
PHILADELPHIA

Insulin and metrazol shock therapy for mental diseases is finding wider application in the hands of investigators. Originally intended for the treatment of schizophrenia, it is now being advocated and used in the management of many other neuropsychiatric conditions. According to Stief and Tokay,[1] insulin is employed in the treatment of neurasthenia, morphine addiction, delirium tremens, exophthalmic goiter, negativistic refusal of food and manic-depressive psychosis, as well as of dementia praecox. Many of the conditions for which insulin and metrazol are used have a comparatively good prognosis with less drastic therapeutic measures. It therefore becomes necessary to study the behavior of these substances in the central nervous system in order to evaluate not only the good which these drugs may do but also the untoward reactions.

Questions which have confronted every worker since the introduction of these two drugs in the treatment of schizophrenia are: Do these substances benefit patients with schizophrenia? Are they capable of doing harm? If they are harmful, of what does the damage to the nervous system consist? It was in an effort to answer the last two questions that this investigation was undertaken.

REVIEW OF LITERATURE

Insulin.—Since the original investigations of Stief and Tokay,[1] in 1932, it has been known that large doses of insulin have a severe toxic effect on animals. These authors showed that the pathologic changes due

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Read by title at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 5-7, 1939.

1. Stief, A., and Tokay, L.: Beiträge zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434, 1932.

to insulin "poisoning" can regress to some extent, but that when larger doses are employed irreversible changes occur. This is important in view of the high doses of insulin that are being used clinically. In their second article on the experimental investigation of the effect of insulin on the central nervous system, Stief and Tokay [2] advised that insulin should not be given without special indication. They noted such severe changes in the brain when larger doses of the drug were given that they warned against the indiscriminate use of insulin and against doses that were too large. Evidence of such universal involvement of the cerebral cortex led them to intimate that greater damage could be done by insulin than by the disease for which it was used.

Grayzel [3] reported the histopathologic changes in the central nervous system of rabbits brought about by the intravenous injection of insulin and the resultant convulsions. He expressed the opinion that the convulsions were the factor instrumental in producing the various types of lesions, which varied from the "milder forms, consisting of zones containing shrunken hyperchromatic cells with corkscrew processes, to the more severe lesions, shown by zones of necrobiosis." Animals which failed to have convulsions, or had only slight ones, showed either minimal or no cerebral changes, whereas animals having severe and prolonged convulsions, if permitted to live long enough, showed extensive and severe cell disease. Grayzel stated that the cerebral lesions were the end result of cerebral anoxemia induced by circulatory disturbance during the convulsions.

Schmid [4] was one of the few investigators using animals who found little or no severe and irreparable damage to the nervous system as the result of injections of insulin in ordinary therapeutic doses. He concluded that the cell changes which were present represented only the early stages of cell disease, and not the "irreversible final stages, with disintegration of the cell body and ringlike formations." Schmid claimed that the changes which he observed were sufficient to explain the clinical picture of a short, recoverable coma or convulsive attack.

Nicolajev,[5] in an experimental study of insulin shock treatment on white rats, observed ganglion cell disease only occasionally in the brain

2. Stief, A., and Tokay, L.: Weitere experimentelle Untersuchungen über die cerebrale Wirkung des Insulins, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:561, 1935.

3. Grayzel, D. M.: Changes in the Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694 (Nov.) 1934.

4. Schmid, H.: Zur Histopathologie der Sakel'schen Hypoglykämieschockbehandlung der Schizophrenie. Vorläufige Mitteilung, Schweiz. med. Wchnschr. **17**:960, 1936; L'histopathologie du choc insulinique, Ann. méd.-psychol. (pt. 2) **94**:658, 1936.

5. Nicolajev, V.: Ueber eine besondere Gliaveränderung nach wiederholten Insulinschocks im Tierversuch, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:205, 1937.

and infrequently in the striatum. The investigations were concerned particularly with the glial changes, and the author noted an increase in glia without relation to the parenchymatous disturbance. In all cases the glia tended to undergo regressive changes, especially after severe shock or a fatal termination. If the shocks were interrupted or induced over a period of many days or if the animals were killed before the development of coma, the regressive changes in the glia were less marked, and frequently the alterations were progressive rather than regressive. Careful study of the liver revealed necrotic foci. The author ventured the opinion that the glial changes in the brain might be the result of damage to the liver.

Weil, Liebert and Heilbrunn,[6] in experimental work on hyperinsulinism, concluded that up to 70 units of insulin given at different periods did not produce microscopically demonstrable damage to the brain, while doses of "from 200 to 400 units injected over a period of two months severely damaged the cerebral neurons."

Tannenberg,[7] in his studies on rabbits treated with insulin shock, observed changes varying from slight to severe degeneration of ganglion cells and reactive glial proliferation. The severity of the changes seemed to depend on the frequency of the shocks and the individual reaction to the drug. They were present throughout the entire central nervous system, including the spinal cord. In cases of severe clinical response almost all the ganglion cells in circumscribed areas of the cortex or of the cornu ammonis had been destroyed. Morphologically, the ganglion cells severely affected by insulin left a "bleached" area in stained preparations.

Confirmatory evidence of the effect of large doses of insulin on the human brain has been given by several authors. The first to substantiate the experimental results of Stief and Tokay was Bodechtel,[8] who observed changes in the cortex which he interpreted as irreversible.

Kobler[9] reported a case of dementia praecox in which a patient aged 24 was treated by the Sakel method of insulin injection. There developed severe convulsions and coma, and the patient died. Microscopic study of the brain showed severe cell disease, with widely

6. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

7. Tannenberg, J.: Comparative Experimental Studies on Symptomatology and Anatomical Changes Produced by Anoxic and Insulin Shock, Proc. Soc. Exper. Biol. & Med. **40**:94, 1939.

8. Bodechtel, G.: Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, Deutsches Arch. f. klin. Med. **175**:188, 1933.

9. Kobler, F.: Histologischer Gehirnbefund nach Insulinkoma, Arch. f. Psychiat. **107**:688, 1938.

disseminated cell sclerosis. Kobler also noted naked cell nuclei as the result of loss of cytoplasmic structure from vacuolation. The parenchymatous changes, with loss of ganglion cells, were not related to distribution of the vessels. The blood vessels themselves were only mildly involved. The author concluded from this study that insulin acts directly on the ganglion cells, without first affecting the blood vessels.

Leppien and Peters [10] reported the case of a patient aged 18, with typical schizophrenia, who died after a dose of 25 units of insulin. At autopsy there was observed diffuse involvement of the ganglion cells of the cortex, particularly in the "central region." The cells were swollen, with no demonstrable Nissl bodies, and appeared pale and homogeneous. The nuclei showed no marked changes, although the nuclear boundaries were frequently not clearly outlined. The cell bodies at times were not sharply demarcated, owing to small vacuolated areas in the cytoplasm, giving the impression of peripheral liquefaction. Cell shadows were noted in the cortex and the basal areas. The striatum, olivary body and dentate nuclei were also involved. An increase in glia was observed in areas in which the ganglion cells were destroyed. In many areas of the brain the ganglion cells that remained showed the picture of ischemic cell disease, with or without incrustation of the Golgi net. Many evidences of simple atrophy could be seen. Occasionally there was separation of the axis-cylinder from the cell. Numerous Purkinje cells were mildly swollen and appeared homogeneous. Shadow cells were present in the Purkinje cell layer. The authors explained these changes on the basis of vascular involvement, plus direct action of the drug on the ganglion cells. The pathologic picture reminded them of the early stages of the acute swelling of Nissl seen in infections and intoxications, and they concluded that the pathologic changes in the brain were the result of the toxic action of insulin. They expressed the belief, however, that it was difficult, if not impossible, to make the diagnosis of a toxic origin.

De Morsier, Bersot, and Le Landeron [11] studied the brain of a morphine addict who was treated with insulin. After one of the injections he slept without taking sugar. He was found the next day in coma, and died in spite of the administration of large quantities of glucose. Histologic examination of the brain showed zones of necrosis with perivascular gliosis.

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10. Leppien, R., and Peters, G.: Todesfall infolge Insulinshockbehandlung bei einem Schizophrenen (klinische und pathologisch-anatomische Beschreibung), Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:444, 1937.

11. de Morsier, G.; Bersot, H., and Le Landeron, H.: Les troubles cérébraux dans l'hyperinsulinémie provoquée, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:101, 1938.

Baker [12] reported 2 cases of spontaneous hypoglycemia terminating in death, in one of which the brain showed diffuse petechial hemorrhages and in the other areas of softening and cystic cavities. On the basis of these 2 cases and of 3 others which he and Lufkin [13] reported, he concluded that hypoglycemia produces severe and permanent damage to the brain, and that similar changes may be produced during the course of insulin shock therapy.

An interesting case was described by Döring [14] in which the patient, aged 29, had received one course of insulin shock therapy and died during a second series of treatments. Examination of the brain revealed hemorrhagic softenings and infarcts. There was diffuse involvement of the cortex, with ischemic and severe disease of the ganglion cells. Döring expressed the opinion that the histopathologic picture could be attributed to vascular changes, such as stasis or spasm of the smaller vessels.

Cammermeyer [15] described the cerebral histopathologic changes in a man aged 37 who died during his fourth insulin shock, induced with only 70 units of insulin. The ganglion cells of the cortex showed severe ischemia and pyknotic changes. The striate nuclei on both sides showed loss of cells. The glia throughout the cerebrum had undergone progressive changes. There were marked vascular congestion, perivascular hemorrhages and hypertrophy of capillary endothelium. Cammermeyer concluded, for much the same reasons as Döring, that the changes in the ganglion cells and glia are probably due to disturbances in the vascular apparatus causing anoxic phenomena.

Metrazol.—Von Meduna's [16] original experimental work in 1934 threw light on the cerebral pathologic lesions associated with convulsions induced by camphor. He claimed that the blood vessels in the nervous system of animals were entirely normal after such convulsions. He described diffuse mild disease of the nerve cells, which he asserted was not dependent on changes in the vessels. He noted that the disease of the nerve cells was most marked in the medulla, and he ventured the opinion that this was evidence of the *Pathoklise* of Vogt.

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12. Baker, A. B.: Cerebral Lesions in Hypoglycemia: Some Possibilities of Irrevocable Damage from Insulin Shock, Arch. Path. **26**:765 (Oct.) 1938.

13. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190 (Feb.) 1937.

14. Döring, G.: Zur Histopathologie und Pathogenese des tödlichen Insulinshocks, Deutsche Ztschr. f. Nervenh. **147**:217, 1938.

15. Cammermeyer, J.: Ueber Gehirnveränderungen, entstanden unter Sakel'scher Insulintherapie bei einem Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:617, 1938.

16. von Meduna, L.: Ueber experimentelle Camphorepilepsie, Arch. f. Psychiat. **102**:333, 1934.

Stender [17] carried out experiments with metrazol on animals. He used 3 rabbits and 2 cats. The brains were examined histologically after from two to thirty-two convulsive attacks. He could find no changes in the vessels, nor could he observe any evidence of damage to the cornu ammonis, which had been described as characteristic of epilepsy. In an adult cat which had twenty-eight convulsions the brain was normal histologically, and in a kitten with thirty-two convulsions only slight changes were observed in some of the ganglion cells in the cortex and the cornu ammonis. These experiments gave no evidence of irreparable cerebral damage as the result of metrazol convulsions.

Kastein [18] claimed that the effect of metrazol could be determined only on the experimental animal, in view of the fact that human material cannot be scientifically controlled. In his experimental study on rabbits he found no effect on the blood vessels, and in this he was in entire agreement with the results of von Meduna's experimental work. He did find involvement of the cellular elements in certain parts of the central nervous system. He noted the greatest damage in the habenular nucleus and in the Purkinje cells of the cerebellum. He also noted sclerosis of ganglion cells of the cortex and basal ganglia, with decrease in size of the cell body and increased stainability. He stated that he did not agree with von Meduna's observation that the cells of the medulla were more affected than the rest of the central nervous system.

Weil and Liebert [19] reported on the effect of metrazol on the central nervous system of rabbits and noted that histopathologic changes occurred only in animals receiving a total of 700 mg. of metrazol or more. They showed that these changes were of mild degree, consisting of shrinkage of the nuclei and cytoplasm of ganglion cells in various parts of the brain.

Comparison of Insulin and Metrazol.—Little work has been done on the comparative effects of insulin and metrazol in the experimental animal. Most authors have concluded that insulin produces greater damage to the central nervous system than metrazol. Even Kastein, although he did not investigate the effect of insulin in experimental animals, made the statement that insulin produces more injury to the brain than metrazol. Our experimental work was undertaken to compare the histopathologic changes in the central nervous system of cats follow-

17. Stender, A.: Ueber Provokation epileptiformer Anfälle durch Cardiazol (Experimentelle und histopathologische Untersuchungen an Tieren), München. med. Wchnschr. **84**:1893, 1937.

18. Kastein, G. W.: Veränderungen in der Form der Neuronen des Gehirnes und des Rückenmarkes bei Kaninchen nach 1,3,5,10,15 Insulten nach intravenöser Injektion von Pentamethylentetrazol, Psychiat. en neurol. bl. **42**:136, 1938.

19. Weil, A., and Liebert, E.: Histopathologic Changes in the Brain in Convulsions Experimentally Induced with Metrazol, Arch. Neurol. & Psychiat. **39**: 1108 (May) 1938.

ing insulin with those following metrazol injections. Particular attention was given to the changes in the spinal cord and posterior root ganglia, in view of the fact that they have received scant attention in previous investigations on experimental and human material.

PERSONAL INVESTIGATIONS

The necessity for thorough investigation of the entire central nervous system was drawn to our attention by the following case.

In a man aged 31 there developed, during the course of insulin shock therapy for schizophrenia, of four years' duration, all the signs and symptoms of fairly advanced multiple sclerosis. According to reliable family and medical sources, he had not shown any disturbance of gait or speech prior to the institution of insulin therapy. During the second week of shock therapy it was noted that the gait was disturbed. The treatment was carried out two weeks longer, with progressive impairment of the central nervous system. When examined by us the patient showed a classic picture of multiple sclerosis, without pallor of the temporal sides of the disks. Whether the multiple sclerosis syndrome was precipitated or brought on by the insulin treatment is an open question.

We have endeavored to duplicate experimentally as closely as possible the usual procedures employed with patients in insulin shock therapy and in the metrazol method of treatment.

MATERIAL AND METHOD

Eighteen cats were employed in this series of experiments. Six animals were discarded because of intercurrent disease, usually sinusitis and encephalitis. Of the remaining 12 animals, 7 were killed by bleeding, 3 died in secondary hypoglycemic shock and 2 died as the result of massive injections of metrazol for purposes of the experiment. Autopsy was performed on all animals immediately, and the brain and spinal cord were fixed for twenty-four hours in a 4 per cent concentration of solution of formaldehyde U. S. P. before gross sectioning.

The animals in the insulin series received increasing doses of the drug in successive intramuscular injections, until evidences of shock appeared within one and one-half hours. As may be seen in table 1, convulsive seizures occurred, but not invariably. Insulin was given on alternate days, except Sundays. The initial dose of 10 units failed to induce shock or even mild evidences of hypoglycemia in the animals. Shock-producing doses varied from 15 to 35 units. The cats appeared to acquire a tolerance to insulin after the first few doses, which were increased by amounts of 5 or 10 units. Shock was terminated by the intravenous injection of from 5 to 11 cc. of a 50 per cent solution of dextrose or by the administration, through a stomach tube, of from 30 to 70 cc. of equal parts of water and Karo (corn) syrup. Three animals died of secondary hypoglycemic shock following injection of insulin three, four and eight hours, respectively, after recovery from shock with the solution of dextrose.

The animals treated with metrazol were given intravenously convulsion-producing doses (which remained fairly constant for each animal) two or three times a week. It may be seen from table 2 that the average dose of metrazol per kilogram of body weight for the cat was greater than that for man. In addition, it will be noted that the average duration, in minutes, of the convulsion

was also considerably greater. The seizures were remarkably similar, in phase and neurologic manifestations, to the human type of grand mal. Cats 8 and 15, in which convulsions were induced twenty-three and twenty-one times, respectively, were killed six and two days, respectively, after the last convulsive dose. Cats 2 and 6, which had twenty and twenty-five convulsions, respectively, were killed four and one-half and three months, respectively, after the last convulsive dose. Cats 16 and 17 were each given a massive dose of metrazol.

After the brains and spinal cords were fixed for twenty-four hours in a 4 per cent concentration of solution of formaldehyde U. S. P., portions were cut for

TABLE 1.—*Data on Cats Treated with Insulin* *

Cat No.	Weight, Gm.	Number of Inductions	Total Units of Insulin	Average Dose of Insulin, Units	Total Amount 50% Dextrose, Cc.	Average Amount of Dextrose, Cc.	Number of Convulsions
5	2,640	2	60	30	10	5	1
7	2,500	7	180	25.7	40	8	5
9	2,920	10	295	29.5	90	9	5

* Shock was induced in these animals after a dose of 15 units of insulin was reached. They became refractory to 20, 25 and 30 units on several occasions, requiring doses of 35 units for induction of shock.

TABLE 2.—*Data on Cats Treated with Metrazol* *

Cat No.	Weight, Gm.	Number of Convulsions	Total Amount of Metrazol, Cc.	Average Dose of Metrazol, Cc.	Total Number of Minutes of Convulsions	Average Number of Minutes of Convulsions
2	2,500	20	17.3	0.86	135.0	6.75
3	3,300	1	0.8	0.8	5.0	5.0
6	2,420	25	16.4	0.65	180.0	7.2
8	2,400	23	15.2	0.66	139.5	6.07
13	3,000	9	5.3	0.58	61.0	6.77
15	2,800	21	14.8	0.7	102.5	4.8
16	3,000	1	2.5	2.5	8.0	8.0
17	3,100	1	2.0	2.0	10.0	10.0

* Cats 2, 6, 8 and 15 received the full quota of indueed convulsions. Note the average duration of a convulsion with the minimal average dose of metrazol required to induce convulsions, as compared with the values for men. Cats 16 and 17 were given approximately three times the average convulsive dose in order to observe any changes in the central nervous system resulting from a single lethal dose.

pyroxylin, paraffin and frozen section preparations. Toluidine blue, Weil's myelin sheath method, phosphotungstic acid hematoxylin, hematoxylin and eosin, Bielschowsky's stain and scarlet red were used in the study of the brain and spinal cord.

In order to arrive at as nearly perfect a comparative evaluation of histologic changes as possible sections were studied and photographed from similar areas of the cerebrum, cerebellum, brain stem and cord.

The protocols and histologic changes are briefly summarized, as follows:

SUMMARY OF PROTOCOLS AND HISTOLOGIC CHANGES

CAT 2 (metrazol).—The animal received twenty injections of metrazol, with production of convulsions; the average length of the convulsion was six and three-quarters minutes; the average dose of metrazol was 0.86 cc. The animal had two

full term litters of living kittens during the course of the experiment, on April 19 and Aug. 2, 1938. The last convulsion was induced on April 18, 1938. The animal was permitted to live until August 31 (four and one-half months).

The gross appearance of the brain was normal.

Histologic Examination.—The meninges presented no changes. There was no marked morphologic alteration in the ganglion cells of any part of the cortex. There were occasional pyknotic ganglion cells. The cornu ammonis showed negligible changes in the cells of the lamina parietalis. The cells of the basal ganglia, brain stem and cerebellum were normal. The scarlet red stain revealed an occasional mild accumulation of perivascular fat. In the spinal cord the morphologic appearance and number of the cells of the gray matter were normal. The cells in the posterior root ganglia were also normal. The Weil myelin sheath stain demonstrated mild status spongiosus in the periphery of the cord. There was no disturbance of the blood vessels.

CAT 3 (metrazol).—The animal received one injection of 0.8 cc. of metrazol; the convulsive seizure lasted five minutes, and the animal died one-half hour later.

Gross examination of the brain revealed congestion of the cerebral vessels. The lungs were congested and showed subpleural petechial hemorrhages. The other viscera presented no gross changes.

Histologic Examination.—There was congestion of the vessels of the entire brain. The morphologic appearance and arrangement of the ganglion cells throughout the brain were not disturbed, except for occasional pyknotic cells in the lamina parietalis of the cornu ammonis and the peripherally situated Purkinje cells in the cerebellum. This has been encountered in normal control cats.

CAT 5 (insulin).—The animal received two shock-producing injections of insulin. The first consisted of 20, the second of 40, units. In the second shock the animal showed convulsive movements one and a quarter hours after the injection. Five cubic centimeters of dextrose, given intravenously, brought about prompt recovery. The animal died, however, three hours later, in secondary hypoglycemic shock.

Gross examination of the brain and cord revealed general congestion and edema.

Histologic Examination.—The cortex showed marked diminution in the number of ganglion cells, particularly in the large cells of the motor area. There were all stages of severe cell disease, including homogenization of Nissl substance, vacuolation, liquefaction necrosis and formation of shadow cells. The same type of change could be seen in the basal ganglia, the brain stem and the cerebellum. In some areas the cells showed pyknosis. In the cornu ammonis moderate degenerative changes of the cells were seen in the lamina parietalis. The scarlet red stain revealed undue accumulation of perivascular fat in both the cortex and the subcortex. The Bielschowsky stain showed various stages of degeneration of axis-cylinders in both the brain and the cord, with clumping of neurofibrils in many of the ganglion cells of the cortex.

Sections of the spinal cord stained with hematoxylin and eosin, the Weil myelin sheath method and phosphotungstic acid hematoxylin revealed status spongiosus. The anterior horn cells were greatly diminished in number and displayed all forms of severe disease. The cells of the posterior root ganglia showed marked vacuolation, karyorrhexis and shrinkage of the capsular nuclei.

CAT 6 (metrazol).—The animal had twenty-five convulsive attacks; the average duration of each convulsion was seven and two-tenths minutes; the average dose

of metrazol was 0.65 cc. The last injection was given on June 27, 1938. The animal was permitted to live until Sept. 20, 1938.

Gross examination showed no visible changes in the brain or the spinal cord.

Histologic Examination.—The meninges were slightly thickened. The ganglion cells in the motor area were normal. There was occasional pyknosis of the smaller ganglion cells in lamina III throughout the cortex. There was mild increase of glia in the cortex and the subcortex. The cornu ammonis showed no pathologic change. The basal ganglia, pons and medulla presented a mild increase of glial elements. Some of the Purkinje cells in the peripheral folia were pyknotic. Mild status spongiosus was noted at the periphery of the spinal cord. The anterior horn cells were normal in number and showed an occasional increase in intensity of staining. The large blood vessels were normal. The small blood vessels presented slight prominence of the endothelium.

Cat 7 (insulin).—The animal received seven shocks; the total number of units of insulin given was 180; the average dose was 25.7 units; the number of convulsions was five. The initial dose of 10 units of insulin failed to produce coma. The next dose of 20 units produced drowsiness and weakness of the limbs. Coma and convulsive seizures were not produced until 30 units was employed. The animal responded promptly after the intravenous injection of a 50 per cent solution of dextrose. After the last shock it died in secondary hypoglycemic shock.

Gross examination showed intense congestion and edema of the brain and spinal cord.

Histologic Examination.—The entire cortex presented profound loss of ganglion cells. Many of the ganglion cells showed vacuolation, formation of shadow cells and liquefaction necrosis; others presented occasional sclerosis and homogenization of the Nissl substance. The glia in the cortex and the subcortex was moderately increased. In the occipital lobe were occasional minute petechial hemorrhages. In the cornu ammonis was moderate evidence of early cell degeneration. The scarlet red stain showed an increased amount of perivascular fat. The Bielschowsky stain revealed disturbance in the axis-cylinders, as shown by loop and spiral formations and clubbing. The cerebellum, pons and medulla showed severe cell disease and loss of cells. The glia had undergone regressive changes in many instances. In the spinal cord there was a marked status spongiosus. The anterior horns had marked loss of cells. The remaining cells displayed cloudy swelling, vacuolation, liquefaction necrosis and formation of shadow cells. There was evidence of degeneration of axis-cylinders.

Cat 8 (metrazol).—This animal had twenty-three convulsive attacks; the average length of a convulsion was six minutes; the average dose of metrazol was 0.66 cc. The animal was killed six days after the last convulsive attack.

Gross examination of the brain and spinal cord revealed a normal appearance.

Histologic Examination.—The meninges were normal. The appearance of the cortex throughout was within normal limits, although in the premotor and occipital areas an occasional pyknotic ganglion cell was seen. In the basal ganglia and the brain stem the ganglion cells presented nothing abnormal. An occasional Purkinje cell showed intense staining and shrinkage. There was mild congestion of the vessels, but no changes in their walls. The vessels of the cord were slightly congested. The anterior horn cells were normal in number and morphologic structure, although an occasional cell was pyknotic. The cells of the posterior root ganglia appeared normal.

CAT 9 (insulin).—This animal received ten injections of insulin, with nine shock reactions and five convulsive seizures. The average dose necessary to produce shock was 29.5 units. The total amount given was 180 units. The cat usually responded promptly to intravenous injection of dextrose; however, after the last shock reaction it died in secondary hypoglycemic shock.

Gross examination of the brain and spinal cord showed congestion and edema.

Histologic Examination.—The meninges were congested. In the motor area the ganglion cells were greatly diminished in number. Many shadow cells and cells undergoing vacuolation and liquefaction were seen. Some of the cells showed pyknosis and sclerosis. There was universal increase of glia. In the temporal lobe many of the cells had undergone a considerable degree of pyknosis, and the remaining cells showed cloudy swelling and severe disease. The basal ganglia and brain stem revealed various stages of severe cell disease. Diminution in number, vacuolation and liquefaction of the Purkinje cells were seen in the cerebellum. The cells of the inferior olive were markedly vacuolated. The spinal cord presented varying degrees of status spongiosus. The anterior and posterior horns had suffered loss of cells. The motor cells showed varying stages of severe disease. The cells of the posterior root ganglia displayed vacuolation, shrinkage and liquefaction.

CAT 13 (metrazol).—Nine convulsions were induced in this animal; the average dose was 0.58 cc.; the average length of a convulsion was seven minutes. The animal had a sinus infection and died seven days after the last convulsion.

Gross examination showed that the brain and cord were normal.

Histologic Examination.—The meninges presented no pathologic changes. The cerebral cortex showed occasional cell sclerosis and hyperchromatic staining, but in the main there was comparatively little change. In the region of the basal ganglia a few small vessels displayed perivascular cuffing with lymphocytes. In the medulla and pons there was moderate congestion of the vessels, in which polymorphonuclear leukocytes could be seen. The region of the cornu ammonis was essentially normal. In the cerebellum, some of the Purkinje cells were pyknotic, but in the main the cell structure was intact. In the spinal cord the anterior horn cells showed little change. Occasional cells were chronically diseased. The cells of the posterior root ganglia showed occasional pyknosis, but there was no evidence of severe cell disease.

CAT 15 (metrazol).—Twenty-one convulsions were induced; the average dose of metrazol was 0.7 cc.; the average length of a convulsion was four and eight-tenths minutes. The animal was killed forty-eight hours after induction of the last convulsion.

Gross examination showed the brain and spinal cord to be normal.

Histologic Examination.—The meninges were normal. There was no disturbance in the architecture or the morphologic structure of the cortex. In the hypothalamic region some of the ganglion cells appeared sclerotic, but not in greater numbers than in the normal cat. In the cerebellum, there was occasional pyknosis of Purkinje cells, particularly at the periphery of some of the folia. The midbrain, pons and medulla showed no disturbance of the cells. The large vessels were entirely normal. Some of the medium vessels showed an early hyaline change. The spinal cord presented no abnormal changes in the gray or the white matter.

CAT 16 (metrazol).—One convulsion, with 2.5 cc. of metrazol, was induced. The convulsion was severe, lasting eight minutes, and the animal died twenty-two and a half minutes after the injection.

Gross examination of the brain showed intense congestion of the blood vessels and edema.

Histologic Examination.—The vessels of the entire central nervous system were considerably congested. No hemorrhages were seen. Throughout the cortex the ganglion cells showed no disturbance, either in number or in structure. In the hypothalamic region pyknosis of the cells was seen; however, this was also observed in normal control animals. In Sommer's sector the capillaries and venules were congested, but the cellular components were not involved. Occasional Purkinje cells displayed mild vacuolation. In the pons and medulla some of the cells showed evidence of cell shrinkage and hyperchromatic staining. Aside from the intense congestion of the vessels, the medulla did not present any pathologic change.

CAT 17 (metrazol).—The animal had one convulsion, induced with 2 cc. of metrazol. It died ten minutes after the injection, during the convulsion.

Gross examination of the brain and spinal cord showed considerable congestion of the vessels of the pia.

Histologic Examination.—The vessels of the pia and those in the cortex and subcortex showed intense congestion, but petechial hemorrhages were not seen. The cerebral cortex and the basal ganglia displayed no disturbance in the ganglion cells, either in number or in morphologic structure. An occasional Purkinje cell showed mild vacuolation, but there was no change in the arrangement or nature of the Nissl substance. In the midbrain, pons and medulla there was congestion of the vessels, but no other change. The stain for fat (scarlet red) revealed slightly more perivascular fat than normal. The Bielschowsky stain showed no disturbance in the axis-cylinders or ganglion cells. In the spinal cord there was intense congestion of the vessels, but no hemorrhage. The cells in the anterior and posterior horns were preserved. In the posterior root ganglia there was no evidence of change in the cells or capsules. The Bielschowsky stain showed no damage to the axis-cylinders.

COMMENT ON HISTOPATHOLOGIC CHANGES

Study of the cerebral cortex of the animals which received convulsive doses of metrazol showed practically no change as compared with the cortex of the control animals. As can be seen from figures 1 *B* and 2 *B*, there was no disturbance in the cortical architecture. The ganglion cells stained clearly. The nucleus did not show distortion or dislocation. The Nissl substance was well differentiated. Shadow cells were occasionally seen, but not more often than in the control animals. The blood vessels stood out clearly and were moderately congested but here again the difference between this picture and that in the control animals was so slight as to enable us to conclude that the cortex of the animals given metrazol was within the normal realm.

In figures 1 *A* and 2 *A*, representing the cortex of a cat that received two doses of insulin, the ganglion cells stained poorly and showed evidences of definite degenerative changes, particularly vacuolation. This is in striking contrast to the cortical picture following injection of metrazol. Considerably more shadow cells were present in the cortex

of the animal receiving insulin than in that of the animal receiving metrazol. The cortex of the animal given insulin showed, in addition, a definite decrease in the number of ganglion cells. The Nissl substance was indistinct. The nuclei did not stand out clearly, and the entire cell picture gave evidence of a severe destructive process. The blood vessels were not prominent. This is of interest in view of the supposition that

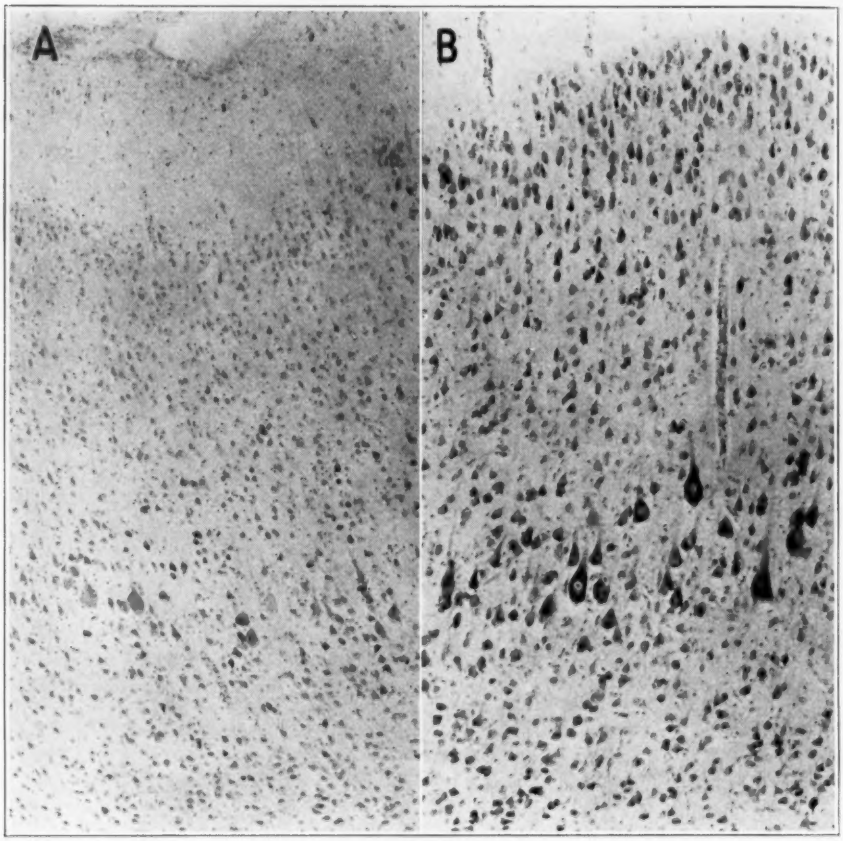

Fig. 1.—Sections of the motor cortex. *A* was taken from an animal receiving insulin (cat 5). *B* was taken from an animal (cat 17) which received one huge dose of 2 cc. of metrazol intravenously, causing death. Note in *A* the diminution in the number of cells, particularly in lamina V, and the severe cell disease, as shown by shadow cell formation, vacuolation and liquefaction necrosis. In contrast to this, *B* shows a relatively normal cortex, with preservation of the normal morphologic appearance of the cells. Toluidine blue; × 82.

with insulin the effect on the cortex is through the blood vascular system (Stief and Tokay).

With more prolonged insulin and metrazol therapy the appearance of the cortex in the two animals (figs. 3 *A* and *B* and 4 *A* and *B*) again

differed greatly. In a cat receiving insulin (figs. 3 *A* and 4 *A*) the ganglion cells were decreased in number; they stained poorly; many shadow cells were visible, as well as remnants of cells that were almost completely destroyed; the glia was slightly increased. The blood vessels were visible, but did not show evidence of endarteritis. In contrast to

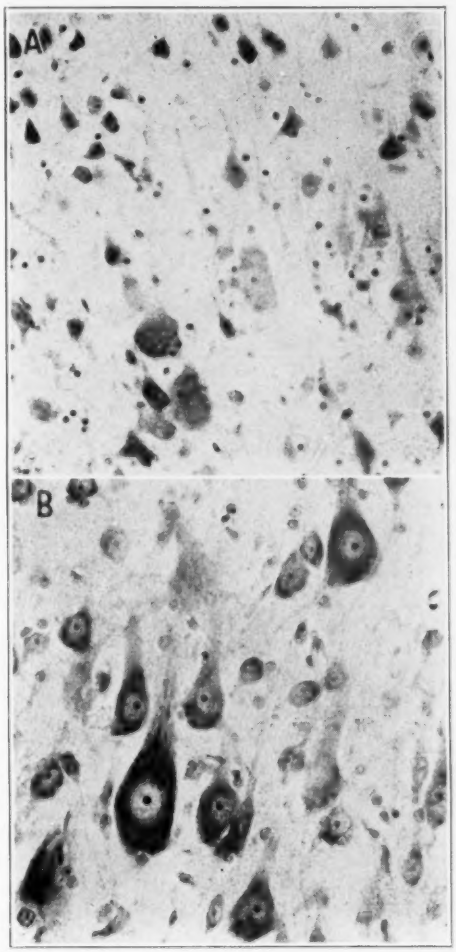

Fig. 2.—*A*, higher magnification of a portion of the section shown in figure 1 *A*, illustrating details of severe disease of the ganglion cells of the cat receiving insulin. *B*, detail from figure 1 *B*, indicating the normal Nissl substance and nucleolar structure of the ganglion cells of a cat given metrazol. An occasional shadow cell is seen, but not as frequently as in *A*. Toluidine blue; × 400.

the cortex of the cat receiving insulin, that of a cat receiving metrazol (figs. 3 *B* and 4 *B*) was practically normal. The ganglion cells stood out in marked contrast to the pale, indistinct, indefinite cells in the

cortex of the cat treated with insulin. The glia of the cortex was not increased after the metrazol treatments.

In figures 5 *A* and *B* and 6 *A* and *B* we have compared similar areas of the cortex from a cat which had seven injections of insulin and died in secondary hypoglycemic shock with those from a cat which had twenty injections of metrazol and was permitted to live four and one-half months.

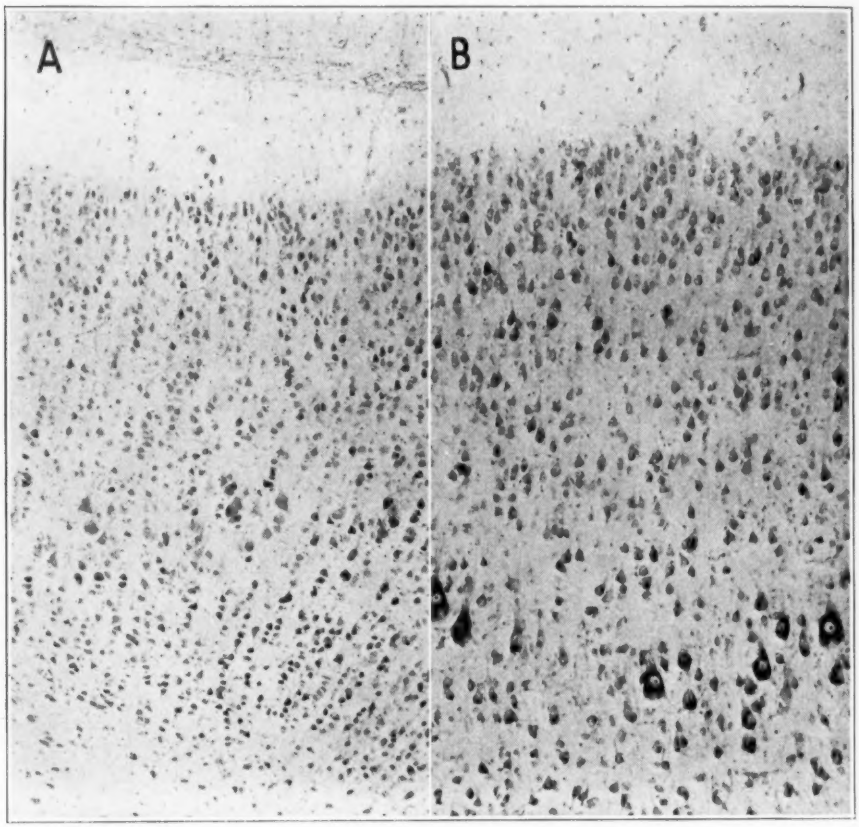

Fig. 3.—*A*, motor cortex of an animal given insulin (cat 9), with ten inductions of shock, showing loss of cells, shadow cell formation, vacuolation, liquefaction necrosis and pyknosis. There is a moderate increase of glia. *B*, similar area of the motor cortex of an animal (cat 15) which received metrazol, with induction of twenty-one convulsions, and which was killed after the last induction. Note the relatively normal morphologic appearance and number of cells. Toluidine blue; × 82.

The difference in the two brains was again radical. In the animal receiving insulin (figs. 5 *A* and 6 *A*) there was a remarkable decrease in the number of ganglion cells; those that were present stained indistinctly;

the Nissl substance was usually homogeneous; the nuclei did not stand out definitely; the processes were visible for considerable distances; many shadow cells were seen. The glia appeared to be increased, but the vessels were not affected to any great degree. In contrast to these are

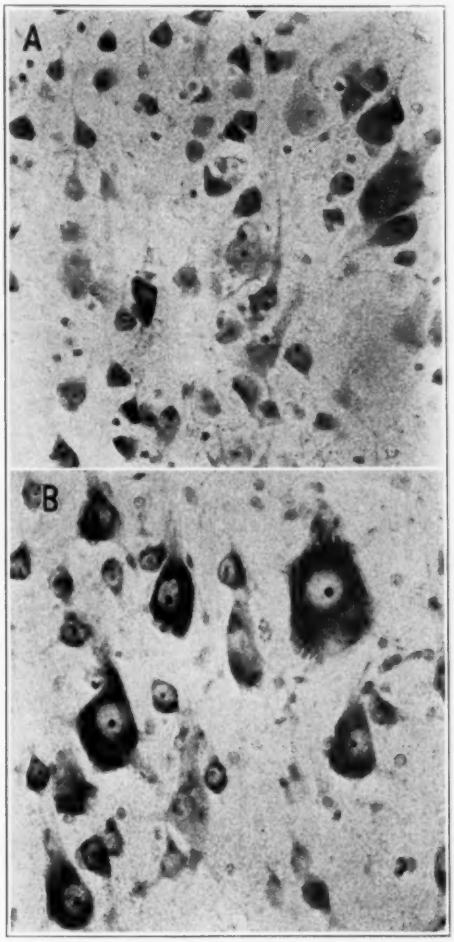

Fig. 4.—Higher magnification of the sections shown in figure 3. Note the severe involvement of the ganglion cells in *A*, as compared with the relatively undisturbed cells in *B*. Toluidine blue; × 400.

the sections shown in figures 5 *B* and 6 *B*, taken from a similar area of the cortex of a cat which had twenty injections of metrazol and was killed four and a half months after the last injection. This cortex is to all appearances within normal limits. It is interesting that the animals

represented in figures 3 *B* and 5 *B* both received the full course of metrazol therapy. The animal the cortex of which is shown in figure 3 *B* was killed immediately after the last injection of metrazol, and the animal represented in figure 5 *B* was permitted to live four and a half months after the last injection. It will be noted that the changes in the brains of both cats are minor and insignificant. With glia stains it could not

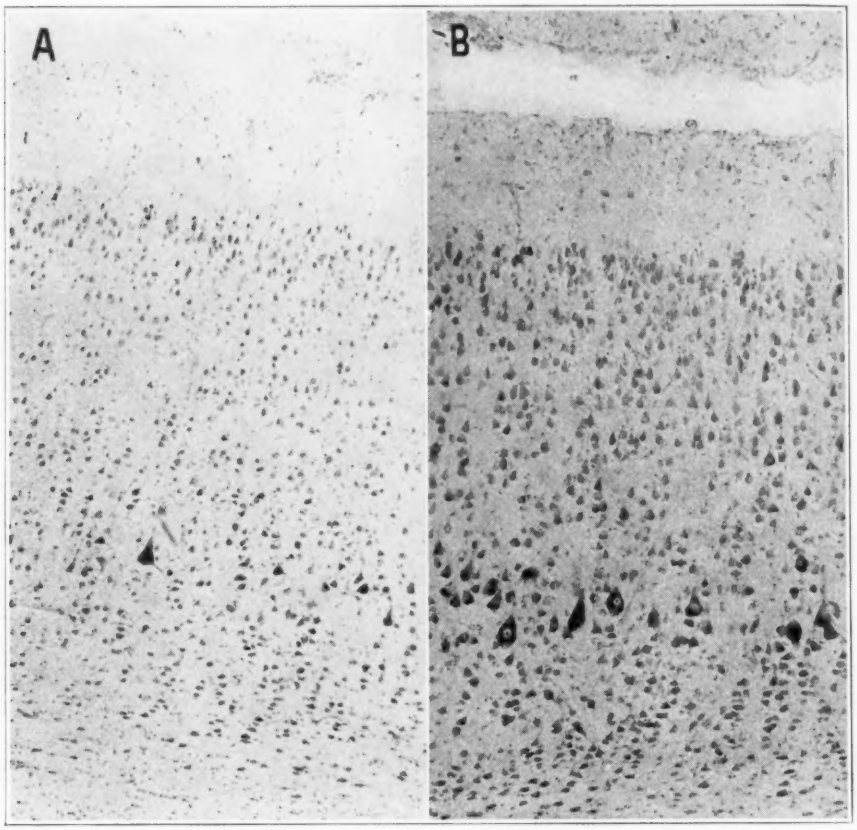

Fig. 5.—Sections of the motor cortex (*A*) from cat 7, given insulin, and (*B*) from cat 2, given metrazol. The latter animal was permitted to live four and a half months after induction of the last convulsion. *A* shows marked devastation of the cortical cells, as compared with the normal appearance of the cells in *B*. In comparing figures 3 *B* and 4 *B* (from an animal receiving metrazol and killed after the last convulsion) with figures 5 *B* and 6 *B* (from an animal permitted to live four and a half months before being killed), it will be seen that the cortex in both animals is within the limits of normal and that in the cortex of the second animal there is no increase of glia elements. Toluidine blue; × 82.

be demonstrated that gliosis was present in either case, even after the animal was permitted to live for four and a half months. Similar observations were made on other comparable animals.

We show for comparison in figures 7 and 8 the sections from the parietal lobe of an animal that received eight doses of insulin (and died of secondary hypoglycemia) and of an animal that received twenty injections of metrazol. It can be readily seen that the cortex from the cat receiving insulin showed widespread destructive changes in the

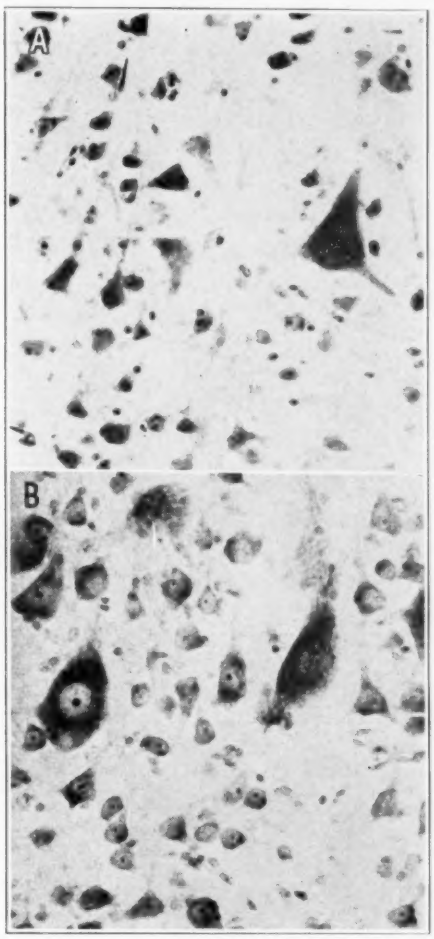

Fig. 6.—Higher magnification of the sections shown in figure 5. Note in *A* (from the cat receiving insulin) the profound changes in the ganglion cells, as compared with the normal ganglion cells in *B* (from the cat receiving metrazol). Toluidine blue; × 400.

ganglion cells, with decrease in their number, in contrast to the cortex of the cat receiving metrazol. As can be seen with high magnification (fig. 8*A*), the cells from the animal given insulin had undergone a

severe destructive process, including vacuolation and liquefaction necrosis. The glia appeared to be slightly increased. A great decrease in cells is evident when this figure is compared with a similar enlargement from the cortex of the cat given metrazol (fig. 8 *B*).

In view of the work of Weil and others, the cornu ammonis was compared in the two series of experiments (figures 9 *A* and 9 *B*). In

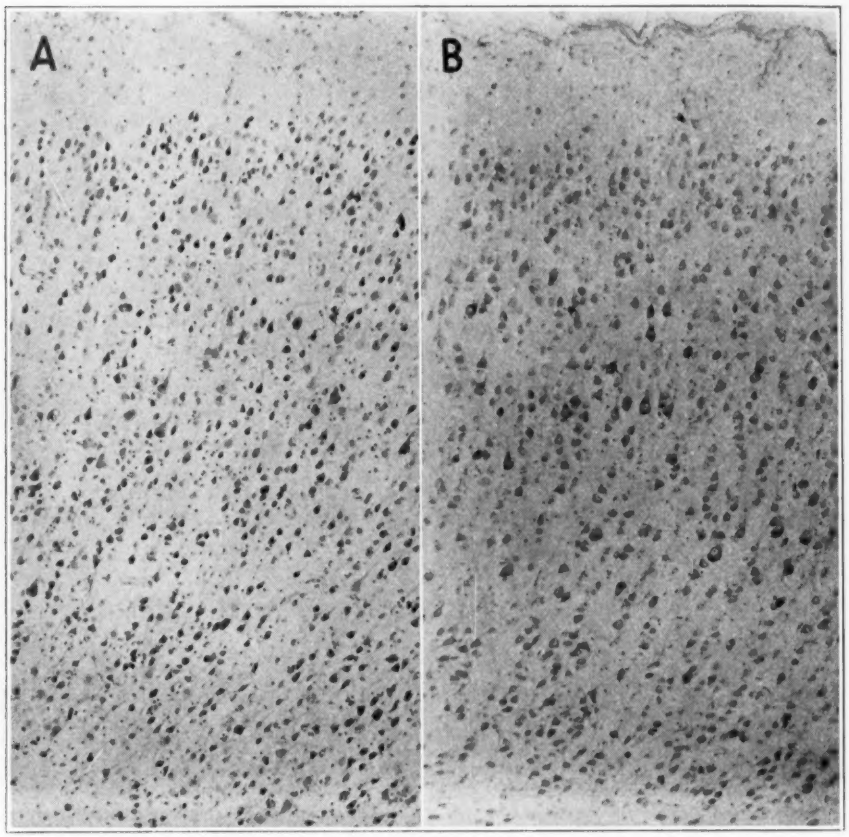

Fig. 7.—Cortex of the parietal lobe (*A*) from cat 9, receiving insulin, and (*B*) from cat 2, receiving metrazol. The cortex in *A* shows small acellular areas, shadow cells, vacuolation, liquefaction necrosis and cell shrinkage. There is also a moderate increase of glia. In *B* it will be seen that the great majority of the ganglion cells maintain their normal structure. No increase of glia is evident. Toluidine blue; × 82.

the animal receiving insulin (fig. 9 *A*) the cornu ammonis showed destructive changes in the cells; many shadow cells could be discerned, although for the most part the involvement of the cortex here was less

marked than in the neocortex. In the cat receiving metrazol there had also been a mild destructive change in the cells, but by no means as marked as that in the animal receiving insulin.

Figure 10 presents a Bielschowsky stain of the cortex and shows the tortuosity and club formation of the axons in a cat after insulin

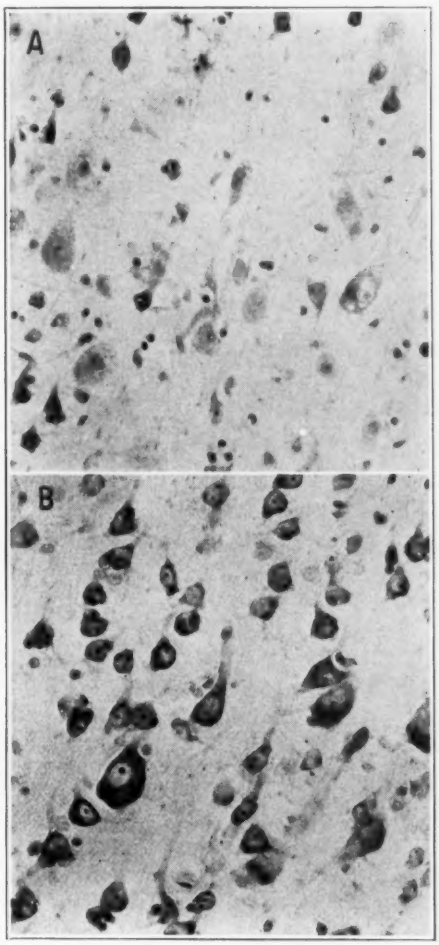

Fig. 8.—High power view of sections shown in figure 7. In *A* the acellular areas shown in figure 7 *A* stand out more clearly and the detail of severe cell disease is manifest. *B* illustrates the comparatively normal-appearing ganglion cells of the parietal cortex in the animal receiving metrazol. Toluidine blue; × 400.

injections. One can see that in the ganglion cells there is clumping of the neurofibrils. In contrast to this, the Bielschowsky picture of the cat in which metrazol convulsions were induced is within normal limits.

In figures 11 and 12 are photographs of the anterior horn of an animal treated with insulin and of an animal treated with metrazol, respectively. In figure 11 the marked destruction and disease of the ganglion cells within the anterior horn can easily be seen. This is in contrast to the normal-appearing cells in the animal given metrazol.

In the high power views (figs. 13 *A* and *B*) the striking differences between the two series of animals are evident. In the cat receiving

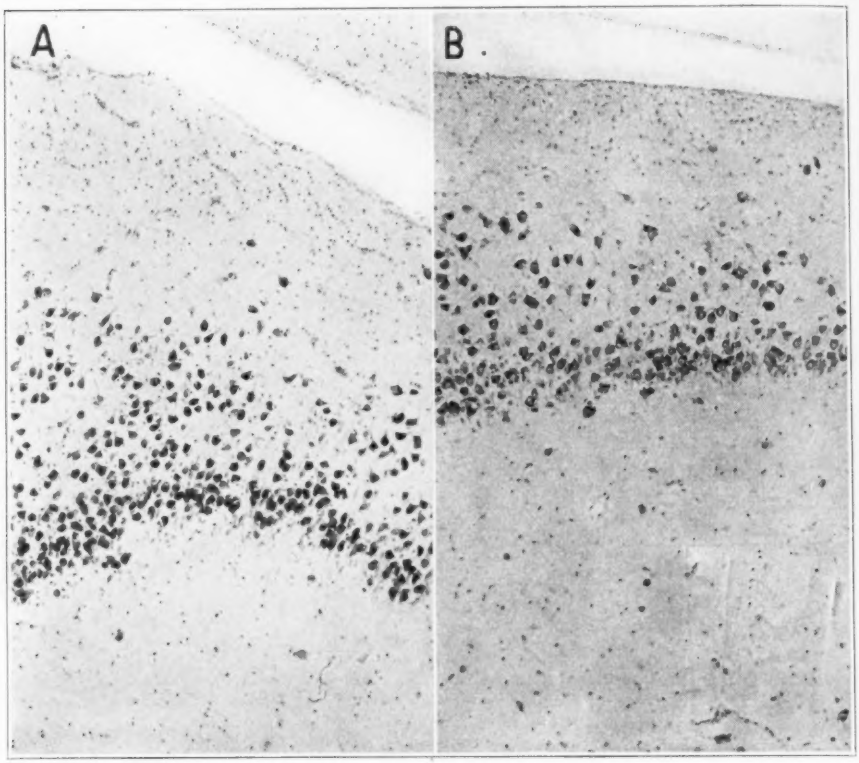

Fig. 9.—Sections of Sommer's sector from the cornu ammonis (*A*) of cat 9, given insulin, and (*B*) of cat 2, given metrazol. Note the early degenerative changes and occasional shadow cells in the lamina parietalis in *A* and the changes of only mild degree in the ganglion cells of the same area in *B*. Toluidine blue; × 82.

insulin the ganglion cells showed an intense destructive process, with vacuolation and occasional formation of shadow cells. Homogenization of Nissl substance was shown in cells that retained some normal appearance. The nuclei in the animal receiving insulin (fig. 13 *A*) were indistinct, and in most of the cells could scarcely be made out. In the

animal receiving metrazol (fig. 13 *B*) the nuclei and cell bodies, as well as the processes, were distinctly and normally stained.

Study was made (fig. 14 *A* and *B*) of the posterior root ganglia both in animals receiving insulin and in those receiving metrazol. The marked difference between the normal-appearing ganglion cells of the

Fig. 10.—Cortex of cat 7, given insulin. Note the degenerative changes in the axis-cylinders: clubbing, tortuosities and swelling. In the lower part of the photograph is a degenerated ganglion cell, with clumping of the neurofibrils. Bielschowsky stain; × 400.

animal receiving metrazol (fig. 14 *B*) and the severely affected ganglion cells of the animal receiving insulin (fig. 14 *A*) was readily discernible. Vacuolation, with gradual disappearance of the ganglion cells, was the

outstanding characteristic of the cells in the animal given insulin. The nuclei became indistinct and eventually disappeared as the cell gradually underwent increasingly severe vacuolation and liquefaction. An eventual decrease in the number of ganglion cells is to be postulated from a destructive action of this kind. In contrast to the normal-appearing

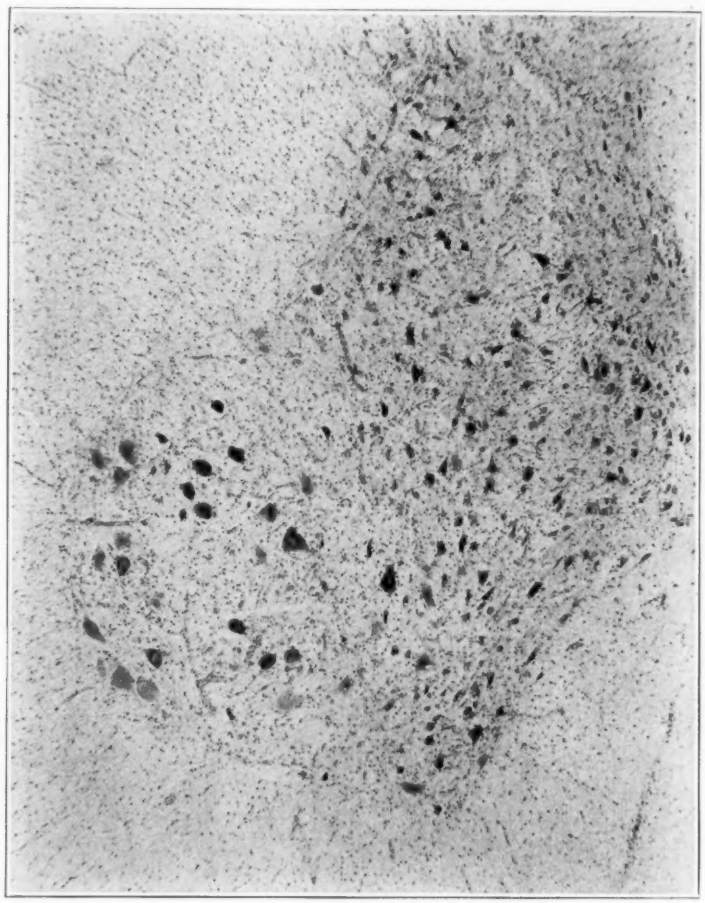

Fig. 11.—Anterior and posterior horns of the spinal cord of cat 5, given insulin. Note loss of cells, particularly in the anterior horn. There are many shadow cells and others with vacuolation, liquefaction necrosis and pyknosis. The glia is considerably increased. Toluidine blue; × 40.

capsular cells of the cat receiving metrazol, the shrunken pyknotic capsular cells of the cat receiving insulin are striking.

Figure 15 represents a phosphotungstic acid hematoxylin preparation of the white matter of the spinal cord from an animal receiving insulin.

The status spongiosus and the slight glial increase are demonstrated. The dilation of the spaces formerly occupied by the myelin sheath and axons resembles to a remarkable degree the change seen in status spongiosus in the spinal cord in cases of pernicious anemia. In the Bielschowsky

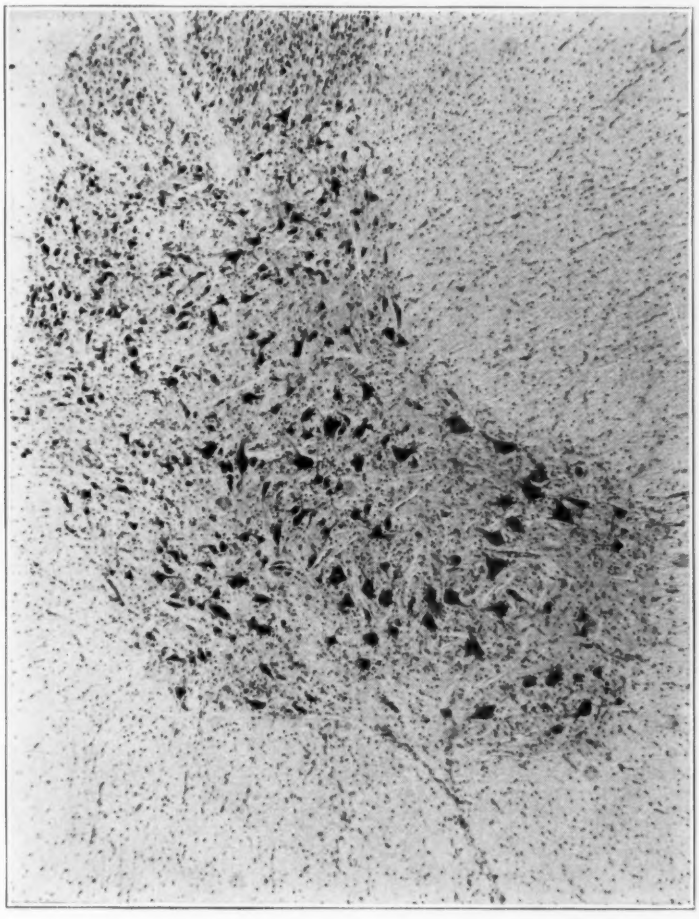

Fig. 12.—Anterior and posterior horns of the spinal cord of cat 2, treated with metrazol. There is no loss of cells, in contrast to the picture in figure 11. The anterior horn cells stand out prominently, and the nuclei are distinct. There is an increase of glia. Toluidine blue; × 40.

preparation of an animal receiving insulin (fig. 16) the dilation of the spaces can be readily seen. Many of the spaces are completely empty; some show swollen, irregular axis-cylinders; others contain

comparatively normal structures. There is a tendency for an occasional axis-cylinder to be swollen and laminated.

It can be stated, in brief, that the central nervous system, including the brain, spinal cord and posterior root ganglia, showed intense cellular

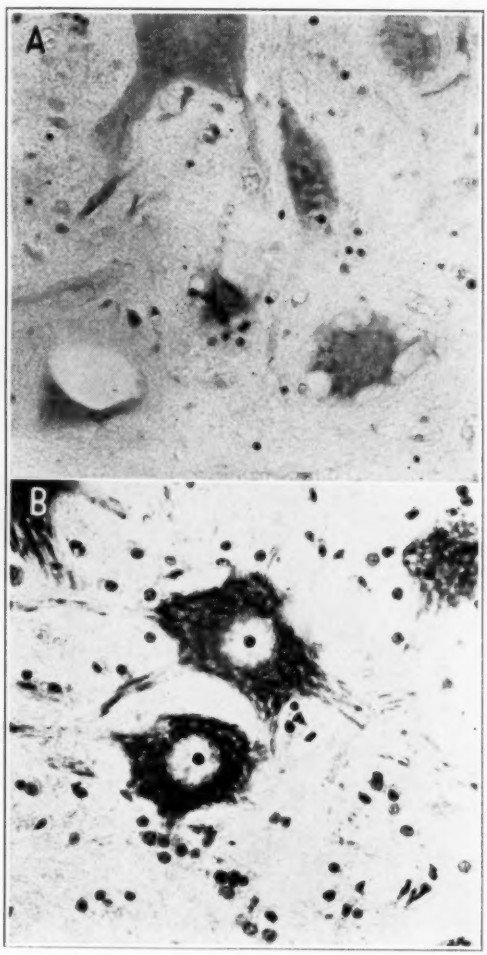

Fig. 13.—Comparable sections of the anterior horn cells (*A*) of cat 9, given insulin, and (*B*) of cat 2, given metrazol. Observe in *A* the evidences of severe cell disease: dissolution of Nissl substance and nuclear structure, vacuolation and liquefaction necrosis. *B* illustrates the complete integrity of the anterior horn cells in the cat receiving metrazol. Toluidine blue; × 400.

degeneration in animals to which insulin was given in a dose sufficient to produce shock reaction over a period, and which died of secondary hypoglycemic shock. In contrast to this, the central nervous system

of animals treated with metrazol was practically normal. The contrast between the two pictures in most instances was striking. It can thus be seen that insulin occasions degenerative changes in the central nervous system which in many instances are not reversible. Whether these

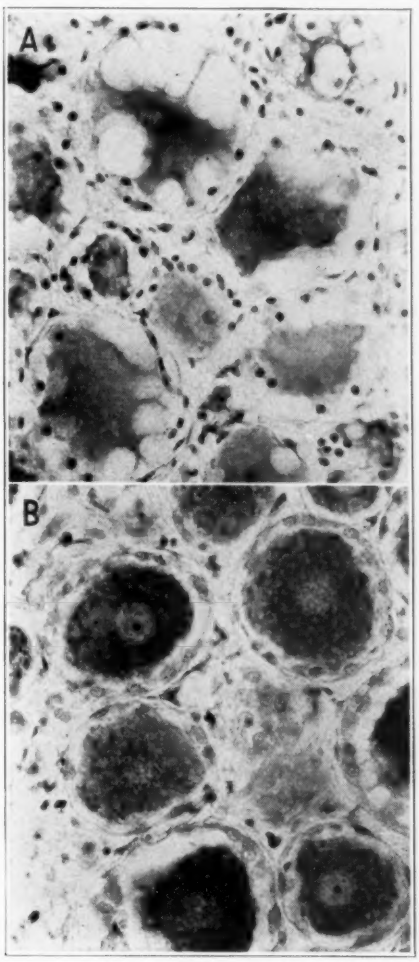

Fig. 14.—Comparable sections of the posterior root ganglia (*A*) of cat 5, given insulin, and (*B*) of cat 17, given metrazol. In *A* the ganglion cells show homogenization of Nissl substance, loss of integrity of the nucleus and nucleolus, vacuolation, shadow cell formation and pyknosis of the capsular nuclei. Compare this picture with that in *B*, in which the cells are essentially normal. Toluidine blue; × 400.

experimental observations can be applied to man has been the basis for considerable discussion in the literature. In cases in which patients have died as the result of insulin treatment the changes in the brain

(Bodechtel) have coincided to a remarkable degree with those described in our experimental animals.

The questions that immediately suggest themselves from a study of the sections are: First, if insulin produces as much damage to the cells of the central nervous system of human beings as has been illustrated

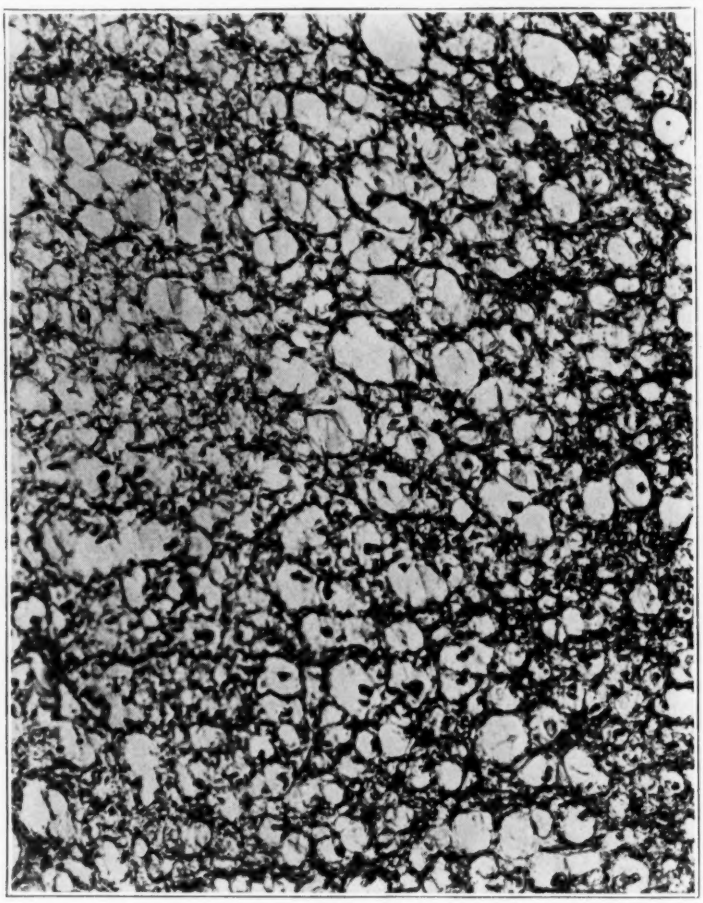

Fig. 15.—Spinal cord of cat 5, given insulin. Note the marked status spongiosus with the "lacelike" structure, similar to that seen in combined sclerosis. Phosphotungstic acid hematoxylin; × 200.

in our cases and in the cases reported in the literature, how does it produce clinical improvement in schizophrenia and other psychoses? Second, are the changes as severe in man as in the animal, and if so is the patient worse after treatment than before? These questions cannot be answered

at this time, but they provoke consideration of the future of insulin shock therapy for schizophrenia and other conditions for which the drug is now being used. In view of the experimental work of Weil and his associates, small doses of insulin are apparently safe, but large doses produce irreparable damage to the central nervous system. Studies in numerous cases of death following hyperinsulinism have shown a change similar to that described in our cats treated with insulin. From this it

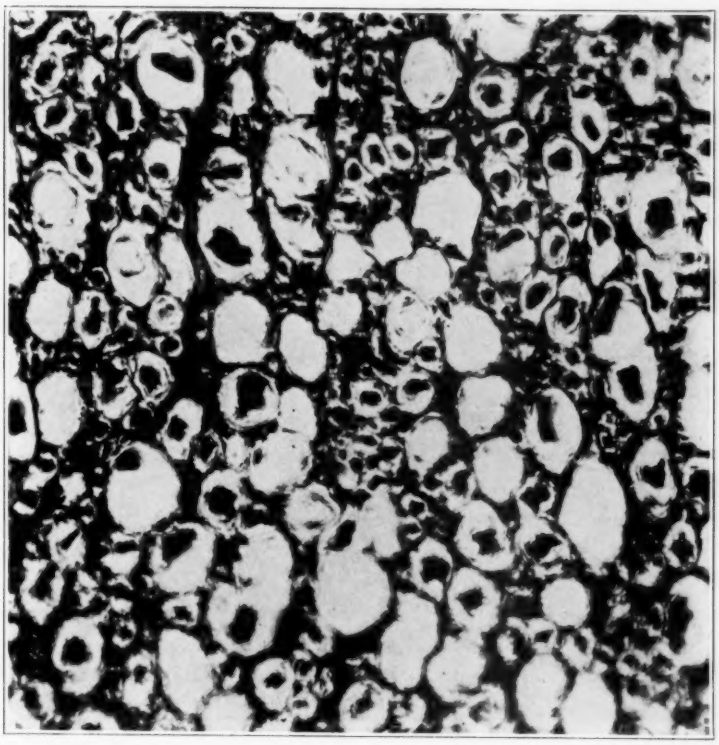

Fig. 16.—Spinal cord of cat 7, given insulin, showing the degenerative changes in the axis-cylinders: swelling, laminar formation and complete destruction. Bielschowsky stain; × 400.

can be stated that when "poisoning" from insulin occurs the changes in man are similar to those in experimental animals treated with insulin reported by many authors and by ourselves. If integrity of the nervous system in animals is any index of the safety of the drug used, metrazol therapy is the safer method, since the changes in the nervous system are slight or insignificant.

SUMMARY

In our experimental work, large repeated shock-producing doses of insulin injured the neurons throughout the central nervous system. From this it is not fair to conclude that in human subjects treated with insulin who have survived histopathologic changes in the central nervous system similar to those demonstrated in our experimental animals have been produced. However, when death has resulted from insulin, the histopathologic changes are comparable with those in our experiments.

The relative absence of involvement of the central nervous system after metrazol convulsions in cats is interesting and important. In addition, the convulsive attacks induced by metrazol in the cat were much more severe and prolonged than in man. Even under conditions such as these, the central nervous system was more or less free from involvement after many convulsive seizures.

In our experiments we could not determine any change in the cornu ammonis comparable with that seen in man after convulsive seizures, as described by the Spielmeyer school.[20] It is possible, of course, that the blood supply in the cat differs from that in man. Uchimura,[21] in a study of the blood supply of the cornu ammonis in man, showed that Sommer's sector is supplied by a single blood vessel, which traverses a long course.

After repeated metrazol convulsions, or after one convulsion produced by an overwhelming dose of metrazol causing death, the ganglion cells in the central nervous system showed little or no change. Von Meduna originally described the most marked changes in the central nervous system as occurring in the medulla. Other investigators have not been able to substantiate this statement. We did not observe any greater change in the medulla than in other portions of the central nervous system.

CONCLUSIONS

An experimental study of the action of insulin and metrazol in the cat has shown that when insulin produces deep shock leading to death severe damage to the neurons occurs, and that with metrazol little if any change in the central nervous system is discernible.

In the brains of animals which died after the administration of insulin, involvement of ganglion cells was manifested by the presence of cell shadows, intracellular neurofibrillar clumping and damage of axis-cylinders. There was also a definite increase of glia.

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20. Spielmeyer, W.: Die Pathogenese des epileptischen Krampfes, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:501, 1928.

21. Uchimura, J.: Ueber die Gefässversorgung des Ammonshorns, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:1, 1928.

In the spinal cord and posterior root ganglia of the animals treated with insulin the changes in the neurons were both quantitative and qualitative, the cells often showing severe disease and in some instances actual destruction.

In the animals given metrazol there were no changes comparable with those seen in the animals given insulin. The changes with metrazol consisted essentially of pyknosis of scattered cells of a minimal degree. There were no quantitative changes. The cell pictures compared favorably with those in the control animals.

If the pathologic changes observed in the central nervous system of experimentally treated cats can be regarded as an index of the ultimate effects in the central nervous system of human beings, insulin in large doses should be used with greater caution and metrazol may be considered the safer drug with respect to the effect on the central nervous system.

HISTOLOGIC VARIATIONS WITH AGE IN APPARENTLY NORMAL PERIPHERAL NERVE TRUNKS

LILLIAN COTTRELL, M.D.
MINNEAPOLIS

The detailed histologic structure of the peripheral nerves has for many years been a matter of investigation and disagreement. Despite all the work that has been done, the variations in the structure of apparently normal peripheral nerves and the alterations of architecture that occur with age have not been clearly established. It is the aim of this investigation to set up a standard for the histologic structure of the peripheral nerves for all decades, so that one may know by comparison what can be considered as abnormal or pathologic. Such histologic changes were studied as could be recognized by simple stains available in every clinical laboratory. The need for such a study has long been apparent from observations made in the neuropathology laboratory of this university in cases in which there was no history of neuritis but in which degenerative changes began in middle age, concomitant with vascular changes, and increased with each decade.

The normal histologic structure of the blood vessels of the peripheral nerves has received little investigative attention. This is unfortunate, since it appears that changes within these vessels may have definite clinical significance. In the latter part of the nineteenth century several pathologists, namely, Schlesinger,[1] Joffroy and Achard[2] and Oppenheim,[3] wrote on neuritis associated with vascular changes in senility. Joffroy and Achard made the observation that just as narrowing and obliteration of arteries in the brain lead to softening so atheroma may produce lesions in nerves. They noted a parallel between the amount of vascular involvement and the degree of degeneration of the nerves. All these men claimed that degeneration was due to lack of nourishment and that the change began in the periphery and progressed centrally.

From the Division of Nervous and Mental Diseases, the University of Minnesota.

Assistance in the preparation of these materials was furnished by the personnel of the Work Projects Administration, official no. 665-71-3-69.

1. Schlesinger, H.: Ueber eine durch Gefässerkrankungen bedingte Form der Neuritis, Neurol. Centralbl. **14**:578, 1895.

2. Joffroy, A., and Achard, C.: Névrite périphérique d'origine vasculaire, Arch. de méd. expér. et d'anat. path. **1**:229, 1889.

3. Oppenheim, H.: Ueber die senile Form der multiplen Neuritis, Klin. Wchnschr. **30**:589, 1893.

Oppenheim noted that it was possible to have marked atherosclerotic changes in vessels of peripheral nerves with little change elsewhere in the body. In more recent years the vascular changes of peripheral nerves have been described in cases of periarteritis nodosa,[4] diabetes and other diseases. The reduced blood supply has been suggested as a contributory cause of the damage to the nerves. In order to evaluate these changes it seems necessary to know the variations that are normally present with increasing age in persons without signs of clinical neuropathy.

TABLE 1.—*Data on 30 Patients from Whom Material for Study of Peripheral Nerves Was Obtained*

Case No.	Decade	Age	Sex	Duration of Illness	Cause of Death
1	1	3 hr.	F	3 hr.	Cerebral birth injury
2	1	3 mo.	F	1 da.	Pneumonia
3	1	2½ yr.	F	2 da.	Bronchiolitis
4	1	3½ yr.	M	1 da.	Pneumonia
5	1	4 yr.	M	2 wk.	Streptococcic meningitis
6	1	9 yr.	M	3 wk.	After operation for tumor of the brain
7	2	12 yr.	M	2 mo.	Leukemia
8	2	13 yr.	M	10 da.	Tetanus
9	2	17 yr.	M	2 mo.	After operation for cerebellar tumor
10	3	20 yr.	F	3 da.	Burns—one-half body surface
11	3	21 yr.	M	2 mo.	Pneumonia; empyema
12	3	21 yr.	F	3 wk.	Abscess of lung
13	3	26 yr.	M	11 da.	Septicemia
14	4	31 yr.	F	2 mo.	Leiomyoma of inferior vena cava
15	4	31 yr.	M	10 da.	Peritonitis following perforated ulcer
16	5	42 yr.	M	2 mo.	Pulmonary embolus after pelvic operation
17	5	48 yr.	F	18 da.	Burns—one-third body surface
18	6	52 yr.	M	3 wk.	Coronary sclerosis
19	6	54 yr.	M	30 da.	Thrombocytopenic purpura
20	6	54 yr.	M	16 da.	Volvulus and peritonitis
21	6	58 yr.	M	6 wk.	Appendectomy; peritonitis
22	7	62 yr.	M	8 da.	Thrombosis of portal vein
23	7	63 yr.	F	10 da.	Incarcerated hernia; peritonitis
24	7	63 yr.	F	3 da.	Pulmonary embolus following operation for cataract
25	7	66 yr.	M	10 da.	Coronary sclerosis
26	7	66 yr.	M	6 wk.	Carcinoma of colon
27	8	71 yr.	M	6 wk.	Carcinoma of pancreas
28	8	76 yr.	M	2 wk.	Hemorrhage from gastric ulcer
29	8	78 yr.	F	7 da.	Bronchiolitis
30	8	81 yr.	M	3 wk.	Generalized arteriosclerosis

METHOD

Nerves were collected at the time of routine postmortem examinations at the Minnesota General Hospital. A section, from 3 to 6 cm. in length, was taken from each of four nerves, namely, the femoral, the median, the sciatic and the common peroneal. The section of the median nerve was procured from the upper part of the arm, where the nerve lies medial to the coracobrachialis muscle and lateral to the brachial artery. The section of the femoral nerve was taken proximal to its passage through the femoral canal, and that of the sciatic nerve, as it passes through the greater sciatic notch, below the piriformis muscle. A segment of the common peronal nerve was removed for a length of several centimeters immediately proximal to its course around the neck of the fibula.

4. Marcus, H.: Perivascular Polyneuritis, Acta psychiat. et neurol. **8**:297, 1933.

The present report is based on a study of 30 cases. These have been selected to exclude clinical evidences of motor or sensory involvement, diabetes or chronic diseases of any sort. Material taken longer than eight hours after death was found to be unsuitable for microscopic study because of autolytic changes. Thus, these 30 cases represent material as nearly normal as it was possible to obtain. Table 1 indicates the distribution as to decades, sex duration of illness and cause of death.

The specimens of nerve were gently stretched on a wooden block as soon as removed in order to avoid distortion during fixation. They were fixed in a solution of formaldehyde. Cross sections were stained with hematoxylin and eosin and by the Mallory-Heidenhain (azocarmine) and Weigert's myelin sheath methods. One case was chosen as representative of each decade for more complete study. The same stains, with the addition of Bielschowsky's stain for axis-cylinders and Weigert's elastic tissue stain, were then applied to longitudinal sections.

RESULTS

First Decade.—This period is represented by cases 1 to 6, inclusive. In cross section the axis-cylinders were irregularly rounded and frequently distorted. In all decades there was marked variation in size. In the newborn the diameters of the axis-cylinders ranged from 1 to 3 microns. Some of them increased in size, until by the age of 4 years the range had widened to from 1 to 7 microns. No increase was noted after the age of 9 years. In longitudinal section the intensity of the stain varied, and irregularities in caliber occasionally occurred in locations other than at the nodes of Ranvier. In the newborn the miniature size of the fasciculus was due not to a small number of the elements but to their individual small size.

Myelin was exceedingly scanty in the newborn. As Duncan [5] has observed, there was an increase in myelination simultaneous with an increase in size of the axon. In the sciatic nerve at the age of 2½ years, from one-third to one-half the fibers were estimated to be myelinated. By the age of 9 years myelination appeared to be comparable with that in later decades. Myelin stained a faint pink with hematoxylin and eosin, a deep pink with azocarmine and black or blue with Weigert's method, but the morphologic pattern was similar with all stains. In cross section the spokelike arrangement radiating from the axis-cylinder was seen, while in longitudinal section the neurokeratin network was clear. With Weigert's stain the fat of the myelin was not dissolved, so that the cross section had less of the geometric, spokelike arrangement. The general impression was that the myelin in the first two decades had a finer, more intricate web than in later decades. The unmyelinated fibers (Remak fibers of earlier writers) were conspicuous in longitudinal sections from the newborn because of their predominance. As compared with the nuclei of the Schwann cells of unmyelinated fibers, those on the myelin sheaths were more frequently rounded and their nucleoli were more conspicuous; the clumps of chromatin were about the same with both types of fibers. The cytoplasm of the cells could be seen only on the myelinated fibers; with hematoxylin and eosin it stained faintly, and then only in the area immediately surrounding the nucleus. A depression of the myelin sheath was frequently observed beneath the Schwann cell.

The connective tissue in this decade comprised less of the substance of the nerve than in the succeeding decades. The fibroblast was by far the most frequent cell of the connective tissue. Other connective tissue cells described in the literature were rarely seen except around blood vessels and could not be

differentiated one from the other with ordinary stains. The epineurium was moderately dense and was evenly distributed in the newborn, but after the age of 2½ years showed a tendency to increase and concentrate in the vicinity of the fasciculi. The fibers were disposed in all directions; the nuclei were rare, and collagen was scanty. Fat, evenly distributed in small quantities, was observed in the sciatic nerve only. The perineurium measured from 6 to 9 microns in thickness and was relatively thin in the first decade. The perineurium, as compared with the endoneurium and the epineurium, was more condensed and contained a larger number of nuclei, more reticulin and less collagen. This was easily demonstrable in sections stained with hematoxylin and eosin as well as with azocarmine.

In case 1 the blood vessels were distended and thus demonstrated clearly the wealth of vascularity. Most of the vessels of the endoperineurium were capillaries, precapillaries and venules, with walls comprised of single layers of endothelial cells. The wall stood out as a thin homogeneous membrane, which stained faintly. Vessels 50 microns in diameter had walls several layers thick, but the cytoplasm still stained faintly. At this diameter the internal elastic lamella began to appear

TABLE 2.—*Range in Thickness of the Walls of Small Blood Vessels* *

Diameter of Vessels, Microns	Thickness of Walls, Microns			
	Decade 1	Decade 2	Decade 3	Decade 4
30	2- 3	4- 6	9-10	10-12
50	4- 5	6- 9	10-14	12-20
75	10-12	9-12	12-16	15-20

* After the fourth decade measurements were too uncertain to warrant tabulation because of the arteriosclerotic changes and consequent encroachment on the lumen of the vessels and a tendency to irregularity in outline of the vessels.

as a thin line, and at a diameter of 75 microns it was a definite structure. A media with well developed muscle was also present and was approximately of the same thickness as the adventitia. The adventitia was made up of loose connective tissue, with longitudinally oriented collagen and a few elastic fibers; it merged with the surrounding connective tissue. The arterioles were largely in the epineurium. The veins appeared similar to those elsewhere in the body, and lymphatics were clearly seen in the epineurium. The weakest place in the vascular system seemed to be in the vessels of the perineurium, for in 2 cases hemorrhages were located in this area. Table 2 shows the thickness of vessel walls in this decade as compared with that in other decades.

Second Decade.—This period is represented by cases 7 to 9, inclusive. The appearance of the axis-cylinders and myelin showed no appreciable changes in this decade from that in the last half of the first decade. No specific measurements of these structures were made, however and it is possible that myelination and the size of the axon were still increasing slightly. No changes were noted in the Schwann cells in this or in any of the succeeding decades.

The connective tissue elements showed only slight changes, which were most marked in the peroneal, less in the sciatic and least in the median and femoral nerves. In the median nerve the epineurium was moderately and evenly dense, whereas in the sciatic and peroneal nerves it was more condensed in the regions adjacent to the fasciculi. The fat present in the sciatic nerve in the first decade

had increased. The perineurium continued to stain intensely, but slightly more collagen was present. The slight increase in the perineurium was most measurable in the sciatic and common peroneal nerves (table 3).

The blood vessels were similar to those of the first decade. As the perineurium became thicker its connective tissue blended with the vessel walls, making them appear, at first glance, like blood-filled spaces. Occasionally these thin-walled vessels were dilated to 20 or 30 microns in diameter, and there was still a tendency to rupture in this location. The epineurium now contained vessels of a diameter of 100 microns or over. The media of these vessels was composed of a small amount of collagen, in addition to the muscle.

Third Decade.—This period is represented by cases 10 to 13, inclusive. The axis-cylinders appeared similar to those in the previous decade. The myelin was also similar, with a slight tendency toward thickening of the spokes apparent in cross section and coarsening of the network in longitudinal section. The anastomosing web showed slight clumping, even in fresh material.

The changes in connective tissue were still progressing. The epineurium had become more abundant and continued to be moderately dense. Fat was now present in the peroneal, as well as in the sciatic nerve. The perineurium was

TABLE 3.—*Range in Thickness of the Perineurium, Showing Increase with Decades*

Decade	Median Nerve, Microns	Femoral Nerve Microns	Sciatic Nerve, Microns	Common Peroneal Nerve, Microns
1	6- 9	6- 9	6- 9	6- 9
2	6-12	6-12	10-14	10-14
3	10-15	10-15	15-20	15-20
4	6-14	6-14	8-18	10-14
5	8-18	6-12	18-24	12-36
6	18-24	8-18	18-30	30-36
7	15-40	15-36	15-40	20-50
8	16-24	24-50	20-60	40-80

still thin but had increased slightly in thickness, as can be seen in table 3. In the second decade there was a beginning tendency for the connective tissue of the epineurium to grow in between the individual fasciculi of the nerve trunk; in the third decade this process had become definite, so that the fasciculi appeared somewhat separated from one another. This epineurial tissue was looser than the perineurium and showed no tendency to regular disposition of its fibers, which were directed at random. These changes were most marked in the peroneal and sciatic nerves. The endoneurium had become more plentiful, and this was well demonstrated with the azocarmine stain.

Vessels were not conspicuous in any of the cases in this decade. Their walls were slightly thicker (table 2), but were comprised of the same elements as previously described. Little collagen and no elastic fibers were seen in vessels under 50 microns in diameter. Even in vessels over 100 microns in diameter collagen was small in amount.

Fourth Decade.—This period is represented by cases 14 and 15. The only notable differences between the peripheral nerves in this decade and those in the previous ones were in the blood vessels and the connective tissue system. The epineurium was increasingly less dense the greater the distance from the fasciculus, and this was more pronounced caudally. Occasionally the perineurium had a highly refractile, homogeneous character, as though hyalinized. The actual thickness of the perineurium, however, was slightly less in these cases than in those in the preceding decade (table 3).

The vessels which were 20 to 50 microns in diameter showed thickening of the walls (table 2). There was an increase in the number of nuclei, and the cytoplasm and nuclei were pale, especially with the azocarmine stain. This proliferation had the appearance of involving primarily the endothelial cells, and occasionally produced partial obliteration of the lumen of the vessel (fig. 1). This process was present in both cases, and in case 14 terminal infection, which might have produced endothelial proliferation, was ruled out as a possible explanation.

Fifth Decade.—This period is represented by cases 16 and 17. The axis-cylinders and the myelin were unchanged, except in areas of replacement with connective tissue, to be described later. The connective tissue continued to follow the trends apparent in the preceding decade. The epineurium was similar except for an increase in fat, which was always most abundant in the sciatic nerve. The perineurium showed a moderate increase in thickness (table 3). It displayed greater

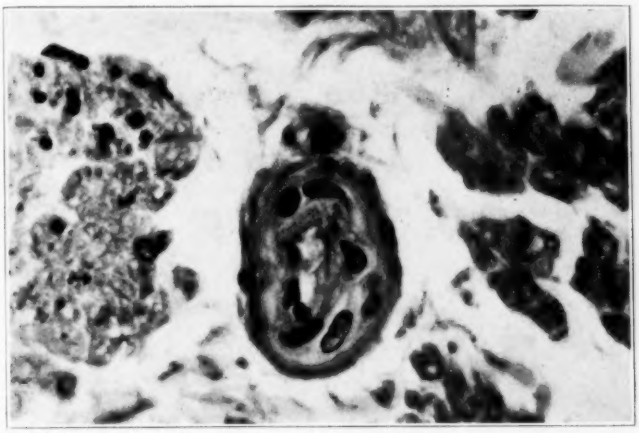

Fig. 1 (case 15).—Cross section of a femoral nerve from a 31 year old patient. The endothelial proliferation is striking and has partially obliterated the lumen of the vessel. Hematoxylin and eosin; × 600.

hyalinization, and stained less pink with azocarmine, indicating more collagen and less reticulin. The vessels had all become thicker. Fibrosis of small vessels of the endoperineurium was especially prominent. Partial occlusion was no longer rare, as in the previous decade. Measurements of thickness of the vessel walls were difficult to summarize because of the wide variation.

In both cases similar areas of altered architecture were seen in the sciatic nerve (fig. 2). The perineurium of the large fasciculus involved in each case was much thicker than in the surrounding normal-appearing bundles. Spraying into the fasciculus from the perineurium was seen connective tissue, with a fine reticulum of poorly stained intercellular substance and small, dark-staining nuclei. Groups of nerve fibers were thus separated into islands by this loose tissue, and degeneration of nerve fibers had obviously occurred. The remaining parenchyma of the fasciculus affected showed clumping of the myelin, with a tendency to form geometric figures, which will be described in connection with a later decade (fig. 5). The axons in these areas, as seen with Bielschowsky's stain, were

swollen and occasionally fragmented. This process was farther advanced in case 17, but was otherwise identical with that in case 16.

Sixth Decade.—This period is represented by cases 18 to 21, inclusive. The changes in the vessels and connective tissue, as well as in the replacements with

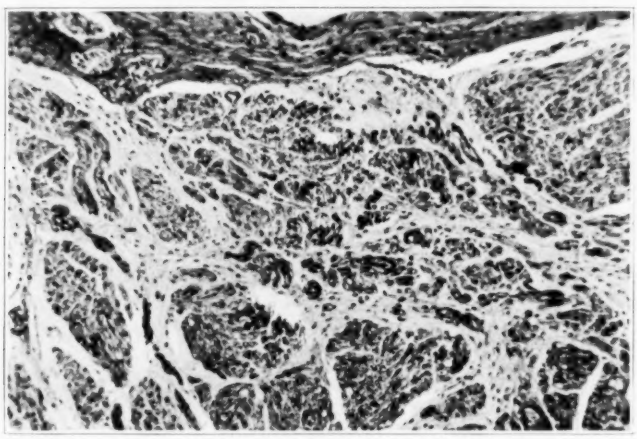

Fig. 2 (case 17).—Area of degeneration in a cross section of the sciatic nerve. Hematoxylin and eosin; × 75.

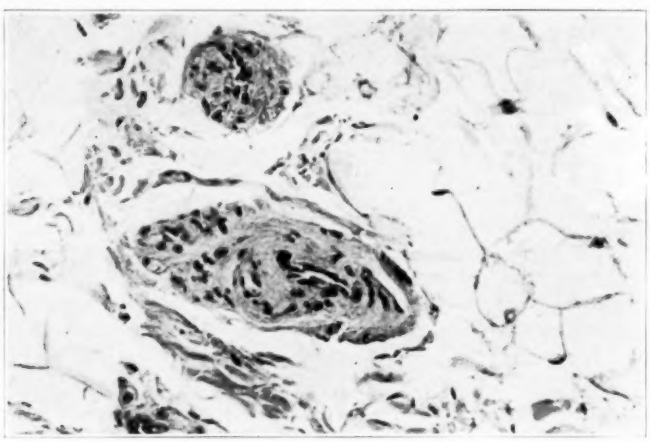

Fig. 3.—Cross section of the sciatic nerve of a person in the sixth decade of life. There is marked medial fibrosis of the wall of the vessels with almost complete occlusion of the lumens. Hematoxylin and eosin; × 250.

connective tissue, presented a variety of pictures in this decade, and are deserving of more detailed description. In the median nerve the epineurium was still moderately dense, with a small amount of included fat. In the peroneal nerve almost all the connective tissue of the epineurium was arranged concentrically

around the nerve bundles. Otherwise the epineurium was similar to that in the previous decade. The perineurium appeared almost totally blue (collagenic) with the azocarmine stain when examined with low magnification. However, with an oil immersion lens the appearance was no longer homogeneous. The blue was seen to be deposited within, or between, the pink cytoplasm which surrounded the nuclei. The noteworthy point is that with increasing years collagen and hyalinization had increased. Except in case 19, a definite increase of the perineurium had occurred in all nerves except the femoral (table 3). In case 19 the perineurium was comparatively thin and averaged 10 microns in thickness.

Two types of change had occurred in the blood vessels. First, endothelial proliferation was similar to that described in the fourth decade, but was more prevalent and frequently caused marked reduction in the size of the lumens of the vessels. The other type was that of fibrosis of the media. With hematoxylin and eosin the vessel wall showed few nuclei and stained a glassy, smooth pink (fig. 3). With azocarmine the deep blue of collagen comprised a large portion of the thickened diameter. This process produced partial obliteration of the lumens in many instances. The fibrosis extended centrifugally as well as centripetally, so that the diameter of the vessels had gradually increased. For example, whereas the vessels of the endoneurial septums had a diameter of 20 to 25 microns in the third decade, they now measured 30 to 50 microns. In some cases both endothelial proliferation and medial fibrosis were present in the same vessel. In case 21 both types of change were present even in the small vessels (from 20 to 30 microns in diameter). In case 18 changes first appeared in the femoral nerve and consisted of endothelial proliferation. In the other 2 cases changes in the sciatic nerve appeared and consisted of intimal proliferation in the small vessels with medial fibrosis only in vessels above 100 microns in diameter. In all cases the changes increased caudally. Again, hyalinization of the perineurium paralleled the increasing thickness of the vessel walls. For example, in case 19, in which the perineurium was the least thick, the vessels showed the least change, and no areas of degeneration were seen.

Areas of degeneration were observed in the sciatic nerves in cases 18, 20 and 21. In case 18 portions of four fasciculi were replaced by whorls of connective tissue, which in turn appeared to be degenerated. These sharply circumscribed areas could be termed infarctions. In case 20 replacement with connective tissue had occurred in several large fasciculi, which was similar to that described in the fifth decade. The replacing connective tissue appeared to be a mixture of young and old elements, and followed the usual distribution of the endoneurium. One third of the parenchyma was estimated to have been replaced in the more involved areas. Several small fasciculi also showed the same reaction, but to a less extent. In case 18 the connective tissue could be seen invading a fasciculus from localized areas of markedly thickened and hyalinized perineurium. The diameter of the bundle in this area was much diminished, and the nerve fibers were interrupted. Changes in axons and myelin in these zones were like those described in the previous decade. No areas of destruction comparable with that in the sciatic were seen in the peroneal nerve; however, there was a perceptible increase in the connective tissue system, with relative decrease of the parenchyma.

Seventh Decade.—This period is represented by cases 22 to 26, inclusive. Changes in vascular and connective tissue continued to increase, but no large localized areas of degeneration were seen. The epineurium continued to be concentrated around the bundles, especially in the sciatic and peroneal nerves. The amount of fat was roughly proportionate to the obesity of the subject. In the

median and femoral nerves the perineurium was comparatively thin, except in case 22, in which it averaged 40 microns in thickness. In the sciatic nerve the perineurium averaged from 20 to 40 microns in thickness and showed marked hyalinization. In case 25 the excessively thickened perineurium had replaced about one half of a large fasciculus. The remaining parenchyma showed some clumping of the myelin. In the peroneal nerves the epineurium and perineurium blended so as not to be definitely separated. In cases 25 and 26 an increase of connective tissue within the fasciculi took different forms. In case 25 the increase was diffuse and moderately dense, with the intercellular collagenous substance taking a medium blue stain with azocarmine. The Weigert stain showed a relative decrease in myelin per field, but the fibers present had normal-appearing myelin. In case 26 the replacing connective tissue was less well developed, stained pale blue, with deep, dark nuclei, and appeared to be degenerating in much the same way as has previously been described.

The blood vessels in all cases showed thickening, but this was more conspicuous in the sciatic and femoral nerves. Vessels above 100 microns in diameter showed

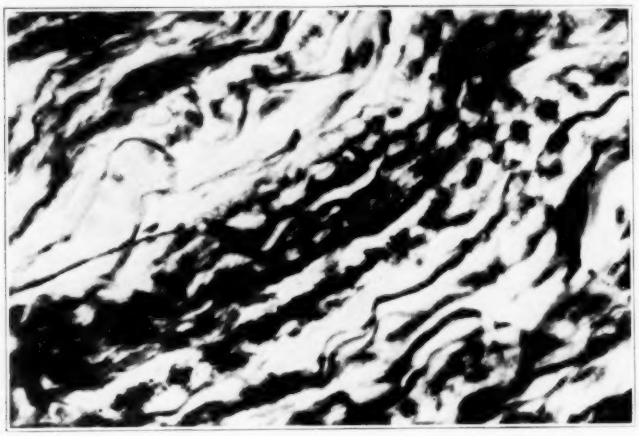

Fig. 4 (case 27).—Longitudinal section of the sciatic nerve of a person in the eighth decade. Note the swelling and irregularity of the axis-cylinders. Bielschowsky stain; × 300.

both intimal and medial changes, which were often observed in the same vessel. Vessels below 100 microns in diameter usually showed only one type of change, that is, either endothelial proliferation or medial fibrosis, but seldom both. In the perineurium, where hyalinization abounded, fibrosis was the major cause of the total or the partial obstruction. The arterioles in this position gave the impression of being squeezed. When total obstruction occurred, the vessel was represented by a hyalinized circle, in which a few dark nuclei were present. The vascular changes were conspicuous in any field.

Eighth Decade.—This decade is represented by cases 27 to 30. The axis-cylinders appeared normal, except that in the areas of degeneration they were swollen, the granules were clumped and a spiral effect was produced (fig. 4). The myelin likewise appeared as in previous decades, except in areas of degeneration. The most spectacular change was that of further concentration and segmentation of the myelin into a series of geometric forms. These were like

truncated cones piled one on top of another, apex to base. The sides of the cones were convex and the bases concave (fig. 5). The less striking modification of the network was coarsening, or perhaps condensation, of the web, with the result that larger strands were seen in longitudinal sections. In cross sections the spokes

Fig. 5 (case 27).—Longitudinal section of the sciatic nerve of a person in the eighth decade of life. Note degeneration of the myelin, with formation of geometric figures. Weigert stain; × 300.

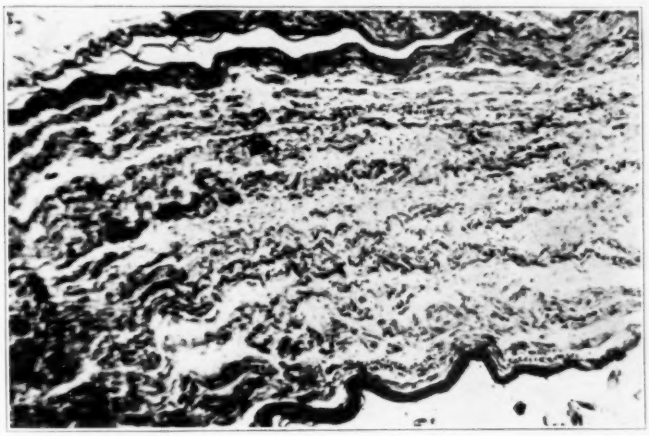

Fig. 6 (case 27).—Longitudinal section of a sciatic nerve from a person in the eighth decade, showing replacement of the parenchyma by connective tissue. Azocarmine stain; × 75.

stained deeper and were fewer and plumper. In case 29 there was diffuse demyelination, which was not seen in the other cases.

Changes in the connective tissue had proceeded in the same directions as have already been described. The perineurium continued to increase in thickness. In

the peroneal nerve the perineurium and the epineurium were now blended to give a dense wall of connective tissue, which measured from 50 to 80 microns. The increase and fibrosis of the endoneurial septums continued.

Changes in the blood vessels were still progressive. Atherosclerosis had succeeded in making the vessels even more conspicuous and the lumens less patent. Occasionally complete obliteration could be seen, with formation of new vessels at the periphery. In case 28 even the veins were hyalinized. The vessels of the endoneurium were less easily seen because they were incorporated in the thickened and fibrosed septums.

Areas of degeneration like those described in the sciatic nerve appeared now for the first time in the femoral nerve, and were similar to those described in the fifth decade. Replacement by connective tissue was still more marked in the sciatic nerve, and such areas were seen in 3 of the 4 cases, with most destruction in case 27. Here, one very large fasciculus and three small ones appeared to be nonfunctioning. A photomicrograph in this case (fig. 6) was taken from a longitudinal section in which the parenchyma had been replaced by young connective tissue, with many nuclei and fine fibrillar intercellular substance. Changes in myelin and axons in sections from the same area are seen in figures 4 and 5. In case 29 similar degenerative areas were seen in several of the small fasciculi. In case 30 the excess connective tissue appeared older and was present in three of fifteen fasciculi. The areas involved were sharply circumscribed; the blue-staining collagen was homogeneous, and the nuclei were fragmented and few.

In the median and peroneal nerves no definite areas of destruction were seen. The impression was still more definite, however, that in the peroneal nerves of persons in this decade there is an actual decrease in the volume of parenchyma, as well as a relative decrease with respect to the connective tissue elements. In case 29 decrease of myelin in the peroneal nerve has already been noted.

COMMENT

The observations made on the relationship of the size of the axon and the degree of myelination seem to support the work by Duncan,[5] who concluded that the presence or absence of the myelin is dependent on the diameter of the axon. Since no systematic measurements were made, the age at which myelination is maximum cannot be stated for the present series. However, in these studies no evident increase in myelination was noted after the age of 9 years, and very little between the ages of 4 and 9 years. This is in accord with the conclusions of Turpin,[6] who stated that by the age of 3 years myelination is fairly complete in the main fiber tracts of the brain.

The exact nature of the neurokeratin network, as seen with tissues fixed in formaldehyde, is not of concern here. According to most investigators, however, it probably represents an artefact. However, if that artefact exhibits alteration with age and degeneration, perhaps it

5. Duncan, D.: A Relation Between Axone Cylinder Diameter and Myelination Determined by Measurement of Myelinated Spinal Root Fibers, J. Comp. Neurol. **60**:437, 1934.

6. Turpin, R.: Evolution anatomique et physiologique du système nerveux de l'enfant, Rev. de méd., Paris **51**:185, 1934.

can be as utilizable as though it existed in the living state. In studying these cases, there was evident a change from the fine delicate network, when first formed at the age of 2 years, to a coarser network, when fully developed at the age of 20 years. This coarse network then became clumped and, with further degeneration in later decades, formed geometric designs.

The most outstanding change with age is that of increase in the connective tissue elements, which is concomitant with reduction of the patency of the blood vessels and destruction of the nerve fibers. Not only do the normal collagenic elements increase, but there is gradual invasion of the nerves by a fine, noncollagenic connective tissue. This replaces normal nerve fibers and itself is degenerated frequently. Myelin and axis-cylinders exhibit degeneration in the surrounding areas. In the fifth decade (ages 40 to 49) these areas of destruction are conspicuous, and, in general, they increase with the succeeding decades.

The endothelial proliferation of the smaller blood vessels begins in the fourth decade and is paralleled by perineurial hyalinization. Medial fibrosis occurs first in the larger vessels in the sixth decade (ages 50 to 59) and gradually increases to involve the smaller arterioles. In the seventh and eighth decades the combination of intimal proliferation and medial fibrosis is so extensive that obliteration and partial occlusion of the blood vessels are commonplace.

There are several possible explanations for the increase in connective tissue. First, the reduction of blood supply may be the cause of death of the parenchyma; also, it may be responsible for the simultaneous increase in connective tissue. Certainly, some of the circumscribed areas of destruction are comparable to infarctions elsewhere in the body. Case by case, the degree of vascular occlusion has paralleled the amount of destruction. Second, changes in the nerve fibers may, of course, result from death of the cell bodies in the spinal cord or the spinal ganglia, which, in turn, may be due to a vascular mechanism operating in those locales similar to that described in the nerves. The increase in connective tissue would then be a secondary phenomenon. The third explanation is that independently of one another vascular occlusion, degeneration of nerve fibers and replacement by connective tissue all tend to occur with age. However, it is likely that all three mechanisms play their role; obviously, they are not mutually exclusive.

The absence of areas of degeneration in the peroneal nerve is not explainable by any available data. Despite the absence of definite areas of destruction, there seems to be an actual decrease in the number of functioning fibers. In 1 case diffuse demyelination even was present.

In spite of the considerable alteration observed within many of the peripheral nerves, especially in the later decades, none of the patients had clinical signs of definite involvement of the nerves. The apparent

adequate function of the peripheral nerves, despite almost complete destruction of fasciculi, has been explained by McKinley.[7] He demonstrated, in the case of the sciatic nerve at least, that the fasciculi fuse and divide throughout the course of the nerve so that many sources of fibers exist for the peripheral bundles. Therefore, any branch of the common peroneal nerve, for example, would be composed of fibers from many fasciculi of the sciatic nerve, and although one fasciculus was destroyed a sufficient number of fibers would remain to give function. In further substantiation of his conclusion that destruction is tolerated, McKinley cited Sherren, who showed that one third of a nerve trunk may be divided without producing permanent motor or sensory changes.

Although the patients in the present series gave no history of definite neuropathy, this study offers an adequate explanation for many of the peculiar complaints of old age. Numbness, tingling, burning and other sensory disturbances, as well as mild motor complaints, may conceivably be due to the histopathologic alterations which have been described. These disturbances are most frequent in the lower extremities, where the peripheral nerves show the greatest degree of pathologic alteration. The added insult of various chronic diseases and toxic agents may well accentuate the already considerable damage to the nerves and result in the well known neuropathies which develop in the later decades.

SUMMARY

1. Histopathologic studies were made of apparently normal peripheral nerves from 30 persons in an attempt to establish the histologic structure of peripheral nerves in the various decades.

2. Definite changes with increasing age were observed in most constituents of the nerves. These alterations consisted more specifically of: (*a*) vascular changes, namely, endothelial proliferation, medial fibrosis and hyalinization, which in the later decades often resulted in complete vascular occlusion; (*b*) connective tissue changes, consisting of a definite increase in the endoperineurium with invasion and replacement of the areas of the nerve bundle by connective tissue elements, and (*c*) parenchymal changes, with alteration and reduction of the nerve fibers. This loss was usually associated with replacement by fibrous tissue.

3. These alterations were most prominent in the later decades of life and suggest an explanation for many of the indefinite motor and sensory complaints of old age.

Dr. J. C. McKinley and Dr. A. B. Baker furnished guidance in these investigations.

7. McKinley, J. C.: The Intraneural Plexus of Fasciculi and Fibers in the Sciatic Nerve, Arch. Neurol. & Psychiat. **6**:377 (Oct.) 1921.

CEREBRAL AIR EMBOLISM AND VITAL STAINING

CONTRIBUTION TO THE EXPERIMENTAL STUDY OF THE BLOOD-BRAIN BARRIER

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In the course of an investigation into the nature of certain forms of damage to the brain from anoxia, cerebral air embolism was produced under controlled conditions in dogs, and was followed in 5 of these animals by intravenous administration of trypan blue. While this work will be reported in its entirety at a later date, the observations in the cases in which vital staining was involved are described here, in so far as they have a bearing on the subject of the hematoencephalic barrier. A general consideration of the physiologic factors involved precedes the description of the experimental phase of the work. Trypan blue was chosen as a dye which seemed to combine most of the essential qualifications for intravital use in a manner most suited to the purpose of this work.

The fact that this dye will not, under ordinary circumstances, pass through the walls of vessels directly supplying nerve tissue has received much attention, but the most comprehensive work and the most recent summary of existing knowledge on the subject have been reported, respectively, by Spatz,[1] in 1933, and by King,[2] in 1939. These investigations were carried out in connection with studies of the blood-brain and blood-cerebrospinal fluid barriers.

The experimental work to which Spatz referred, both his own and that of other investigators, included damage to the nerve cells by toxins and retrograde degeneration, on the one hand, and damage to the vessels by various means, on the other, but with entirely negative results with respect to vital staining of cerebral tissues, except when damage to the vessels was of a degree to cause hemorrhage.

This work was carried out in the Department of Pathology of the Henry Ford Hospital, Detroit; Frank W. Hartman, M.D., Director.

1. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre vom Stoffaustausch zwischen dem Zentralnervensystem und dem übrigen Körper; das morphologische Substrat der Stoffwechselschranken im Zentralorgan, Arch. f. Psychiat. **101**:267-358, 1933.

2. King, L. S.: The Hematoencephalic Barrier, Arch. Neurol. & Psychiat. **41**:51-72 (Jan.) 1939.

The successful experimental work of other authors aiming at vital staining of extravascular, specifically nerve tissues in the brain has so far involved exclusively, as far as I am aware, cerebral lesions in which gross damage to the vessels was a factor,[3] e. g., hot and cold stab wounds, skull fractures and concussions, except for the work of McClellan and Goodpasture,[4] who produced lesions in cats with the virus of herpes febrilis.

King proposed a somewhat divergent explanation of the phenomenon of nondiffusion, pointing out that if Spatz was correct in assuming that the vascular endothelium represents the actual barrier, this would presuppose an essential difference between the endothelium of cerebral capillaries and that of vessels elsewhere in the body. Moreover, within the central nervous system itself a difference would have to be assumed in view of the fact that in the normal choroid plexus the dye passes the endothelium readily to stain the surrounding tissues, but does not pass into the cerebrospinal fluid surrounding the plexus. King expressed the opinion that such a difference was unlikely, as well as unproved to date. Anatomically, a distinction can certainly not be made with present methods.

King concluded that the failure of the cerebral tissues to stain with trypan blue administered intravenously is due primarily to the "unique constitution of the nerve tissue," that is, to lack of "affinity," or "binding power," for the dye. He pointed to an observation by Macklin and Macklin,[3] who noted accumulation of trypan blue in lesions of the brain produced thirty-five days before the injection of the dye, that is, at a time when damage to the vessels, as reflected by excessive permeability to plasma, should have been entirely repaired (in the words of King, "when exudation is negligible"). This would indicate that the reason for the penetration of the dye lies in the changed nature of the extravascular tissue. King also made the statement, however, that "storage of trypan blue in parts of the nervous system where it does not normally take place is dependent on inflammatory or necrotizing changes. Other types of morphologic change are not sufficient to allow vital staining."

Both Spatz and King referred repeatedly to the cerebral cellular elements, both glial and nervous, on the one hand, and to the blood vessels, on the other, and Spatz arrived at his conclusions after studying only the effects of damage to one or the other of these structural units. In his comparison of the differing actions of dyes when applied in differ-

3. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by the Use of Trypan Blue, with Special Reference to the Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. **3**:353-394 (April) 1920.

4. McClellan, R. H., and Goodpasture, E. W.: A Method of Demonstrating Experimental Gross Lesions of the Central Nervous System, J. M. Research **44**:201-206 (Dec.) 1923.

ing ways to brain tissue, he spoke of the latter as behaving like a colloidal mass and compared the manner of penetration of extravascular dye to that in gelatin, but without more specific reference to microscopic structure in relation to this behavior. King's suggestive references to brain tissue as a whole and to its "binding power" for the dye have been cited. Macklin and Macklin, in comparing inflammatory lesions in the brain with those in bone, were struck with the fact that even in the case of injury sufficient to permit vital staining the brain tissue differed from bone tissue in the degree of staining, thus pointing to the presence of a constant differentiating factor.

In an evaluation of the various tissue elements comprising brain tissue, it is found that the bulk of the gray matter, despite its cellularity, is composed of the colloidal "ground substance," in which are embedded all the formed elements. Taft,[5] in a recent report on his extensive work and observations on this ground substance, stressed its role in the metabolic activity, and especially in the water balance, of brain tissue, and von Braunmühl [6] urged a colloidochemical approach to neuropathologic problems. The relative neglect of the nature and behavior of this labile and highly characteristic basic tissue element by investigators working with vital dyes is perhaps due, in part at least, to the more or less chronic nature of their experiments and to attempts to locate the dye microscopically. In the majority of cases animals receiving vital dye intravenously were given large amounts and were kept alive for considerable periods after the first injection, to enable the dye to become flocculated in cell bodies and thus readily visible in microscopic sections.

In this connection, attention is called to the various forms in which vital dye may be present in extravascular tissues, as defined by Spatz, who distinguished three stages: 1. "General diffusion." Both cells and intercellular substance show transient and mild staining of equal intensity. In this form the dye exerts a definite influence on the vital functions of the involved parts. 2. "Granular or vacuolar storage." Necessary precedent conditions are the colloidal or semicolloidal nature of the dye and the passage of time. Such storage occurs only in living cells, and the dye has in this state no longer any effect on the vital functions. 3. "Diffuse staining of cells." In contrast to the granular form of storage, this is an expression of severe cell damage.

In order to demonstrate dye microscopically in the first stage of diffusion, it must have been administered in large quantities, and thick, unstained sections must be studied. The second stage is not encountered

5. Taft, A. E.: Intercellular Substance of the Cerebral Cortex (Nissl's Cerebral Gray Matter), Arch. Neurol. & Psychiat. **40**:313-321 (Aug.) 1938.

6. von Braunmühl, A.: Kolloidchemische Betrachtungsweise seniler und präseniler Gewebsveränderungen. Das hysteretische Syndrom als cerebrale Reaktionsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:1-54 (Sept.) 1932.

in the brains of animals killed within a few days of injection. In the work reported here, trypan blue was given in relatively small amounts and low concentrations, and no animal was kept alive more than forty-eight hours after the first injection, as the main objects of staining were gross demonstration of the mild lesions produced by air embolization and investigation of the behavior of the cerebral ground substance, regardless of the presence or absence of the dye.

Krogh's [7] studies of the endothelium of the extracerebral vascular system revealed that the endothelial cells as such represent only a passive semipermeable membrane. Attention has already been called to the essential similarity of vascular endothelium in the central nervous system and elsewhere. It is, however, an established fact that the cerebral vascular system as a whole differs from other vessels in its behavior toward both drugs (as administered in "physiologic" manner) and various nerve stimuli,[8] in the sense that it cannot readily be made to react and that contraction especially is difficult to produce and is never complete, except as a result of direct mechanical irritation. It is reasonable to consider the nature of the innervation and the degree of vasomotor response as factors quite apart from the degree of permeability of the capillary endothelium for certain substances, except in the limited sense that the ability of the cerebral capillaries to dilate would decide, at least in part, the extent to which they might become temporarily more permeable. Such a change could, moreover, affect permeability only in a general way, without essentially altering any innate specific ability of the endothelium to permit one substance to pass while others are held back.

A highly important factor of differentiation between cerebral and other vessels is to be found in their respective reactions to embolic material. Blood vessels generally contract in spastic manner when irritated by solid intravascular substances, such as powdered pumice or carbon particles, with consequent circulatory disturbances not directly due to the local obstruction by the embolus. Moreover, as Chase [9] has

7. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922.

8. Riser: Les spasmes vasculaires de l'encéphale, J. méd. franç. **26**:228-231 (July) 1937. Golla, F. L.: Some Remarks on the Physiology of the Cerebral Circulation, J. Ment. Sc. **83**:505-508 (Sept.) 1937. Forbes, H. S., and Cobb, S.: Vasomotor Control of Cerebral Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:201-217, 1938. Schmidt, F., and Hendrix, J. P.: The Action of Chemical Substances on Cerebral Blood Vessels, ibid. **18**:229-276, 1938. Fog, M.: Cerebral Circulation: I. Reaction of Pial Arteries to Epinephrine by Direct Application and by Intravenous Injection, Arch. Neurol. & Psychiat. **41**:109-118 (Jan.) 1939.

9. Chase, W. H.: Anatomic and Experimental Observations on Air Embolism, Surg., Gynec. & Obst. **59**:569-577 (Oct.) 1934.

demonstrated on the vessels of the rabbit's mesentery, gaseous emboli produce the same effect. He found that emboli of room air acted as "strong or moderate vascular irritants" and that the effects were "in all respects similar to those produced by other mechanical, chemical or bacterial irritants." Cerebral vessels, on the other hand, appear to be completely indifferent to gas emboli, as Villaret, Cachera and Fauvert [10] convincingly demonstrated in dogs by direct measurement and serial photomicrographs. These authors also determined that such emboli usually disappeared within a few minutes at the most from the original site of occlusion, lasting in most cases only several seconds and in rare instances over one-half hour.

The work and conclusions reported here are based on the double premise of indifference of cerebral vascular walls to air emboli and of the transient nature of such embolization.

EXPERIMENTAL WORK

Methods.—As a preliminary step to animal experimentation, in vitro experiments, based in part on the work of Lenggenhager,[11] were carried out to observe the behavior of gas bubbles in moving fluid mediums under conditions simulating those of the intravascular circulation, as the desired aim was the production of discrete, mild, primarily cortical lesions of one side of the brain only, which would leave the structures of the midbrain and hindbrain intact (to permit continuation of life on a relatively normal level) and avoid as far as possible any damage to blood vessels, with its attendant hemorrhage and other more or less permanent circulatory lesions and alterations.

With the animal under ether anesthesia, from 1 to 2 cc. (occasionally slightly more) of room air was injected in divided doses within a brief space of time into the left common carotid artery of healthy young dogs, just proximal to the origin of the internal carotid artery. The injection was made with a long, flexible, 25 gage needle, introduced in such manner as to interfere as little as possible with the normal current of blood, and with the point of the needle directed toward the orifice of the internal carotid artery. Aseptic technic was observed, and the wound was closed surgically. Trypan blue was injected intravenously in 5 of the embolized dogs at varying intervals after operation and in broken doses, and these animals were killed quickly with large intravenous doses of saturated solution of magnesium sulfate forty-eight hours after operation, except for 2, which died six and twenty hours, respectively, after injection of air. The dye was dissolved in physiologic solution of sodium chloride, rather than in water, in order to avoid as far as possible any aggravation of the cerebral edema which developed to some degree in each case, and which was apparently responsible for the

10. Villaret, M.; Cachera, R., and Fauvert, R.: Spasmes des artères cérébrales provoqués par l'embolie expérimentale du cerveau, Compt. rend. Soc. de biol. **125**:58-61, 1937; L'embolie gazeuse cérébrale: Ses effets circulatoires locaux, ibid. **125**:108-111, 1937. Villaret, M., and Cachera, R.: Les embolies cérébrales: Études de pathologie expérimentale sur les embolies solides et gazeuses du cerveau, Paris, Masson & Cie, 1939.

11. Lenggenhager, K.: Wirkungsweise der Luft- und Fettembolie, Schweiz. med. Wchnschr. **64**:146-150 (Feb. 17) 1934.

premature death of some of the animals. The dye was used once in 0.5 and at all other times in 1 per cent concentration. Greater strengths might have been used, but were avoided so as to render the toxic effect negligible as far as possible. The solution was sterilized before use.

The brains, and in some cases parts of the body organs as well, were removed immediately after death. All the brains were subjected to thorough gross examination, and blocks for embedding were cut in such manner as to permit close correlation of gross and microscopic observations. In 1 case this was of particular importance, as the dye had been given first twenty-four hours after operation so as to permit some degree of recovery of the areas of transient ischemia, on the assumption that if the blood supply had been shut off for only several seconds to a few minutes nerve cells would not be irreparably damaged, and that if this

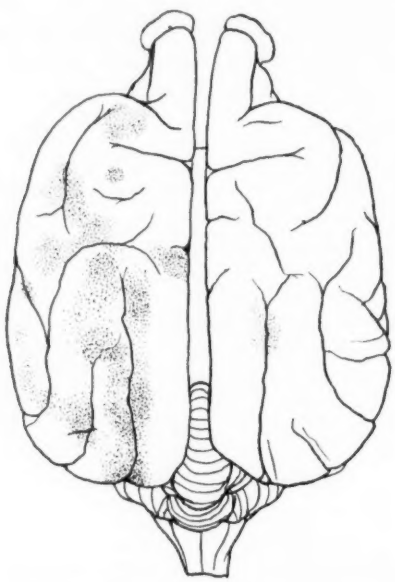

Fig. 1 (dog 12).—Dorsal surface of the brain. The shaded areas indicate vitally stained cortex. The total amount of dye used was 20 cc. of a 1 per cent solution. Death occurred approximately six hours after operation.

The delicate blue of the dye against the gray of the cortex rendered adequate photographic reproduction impossible.

factor were of importance in deciding whether the dye would stain the extravascular tissues one might expect to find the majority of lesions unstained.

All material was fixed in several changes of a dilute solution of formaldehyde U. S. P. (1:10); adjoining blocks were embedded in paraffin and pyroxylin, and sections were stained with hematoxylin and eosin, cresyl violet, Bodian's silver impregnation method and a modification of Weigert's stain for myelin sheaths. Unstained sections were also mounted.

Results.—Gross examination of the brains in every case revealed stained lesions, visible over the surfaces of the hemispheres and in cross sections. Occasionally almost an entire convolution appeared blue, apparently owing to confluence of

smaller, crowded lesions, but in no instance was the entire hemisphere stained, even in cases of marked unilateral cerebral edema. Unstained lesions were not seen even in the animal which received dye only during the second twenty-four hour period after operation, except for two or three areas, all very small, which showed only moderate sponginess under the microscope, but no loss of histologic stainability of the ground substance or cellular elements. This was true despite the fact that practically all lesions in this case were small and mild, corresponding to the neurologic picture during life.

Worthy of note was the remarkable uniformity of all lesions in respect to their behavior toward the dye, regardless of the size of the lesion or, apparently, of at what time after operation the dye had been given.

The pituitary gland and the choroid plexus in all animals were diffusely, although usually weakly, stained, even in the animal which survived the operation only six hours.

The lesions produced were almost exclusively intracortical, were located chiefly in the area of end distribution of the middle cerebral artery, appeared grossly

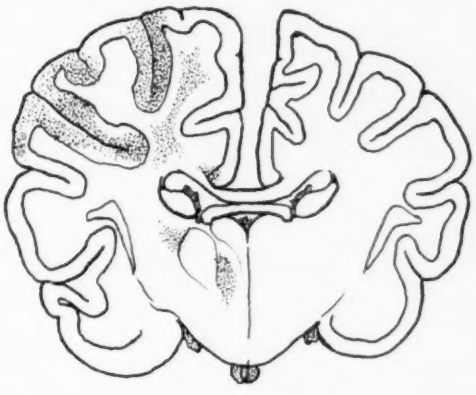

Fig. 2 (dog 12).—Coronal section of the brain. Note the vitally stained areas in the white matter of the hemisphere and in the region of the basal ganglia and diffuse staining of the choroid plexus and the pituitary gland.

as spherical to ovoid, fairly well defined areas of somewhat softer consistency than the surounding normal tissue, and in the great majority of instances did not show hemorrhages, even microscopically. In animals not vitally stained these lesions appeared almost white against the gray of the cortex, while in the vitally stained preparations they appeared a homogeneous pale blue. Many lesions were recognizable only microscopically, in histologically stained sections, although clearly in these. The outstanding characteristics of all lesions in stained sections, both those from animals stained with trypan blue and those from animals which were not, were poor histologic staining of all tissue elements, except usually for the glia cells; varying degrees of rarefaction of the cortical ground substance, and changes in nerve cells ranging from mild ischemic damage (most frequent) to, occasionally, complete disappearance. Blood vessels appeared intact, except in the severe and sometimes hemorrhagic lesions, with evidence only of occasional hypertrophy of endothelial cells. There was in practically no instance more than slight evidence of positive tissue reaction.

This change in ground substance, which appeared to be identical in nature and degree both in animals which were vitally stained and in those which were not, was, in all lesions not associated with hemorrhages, the dominant feature in the microscopic picture and the chief, occasionally even the only, means of locating the lesions.

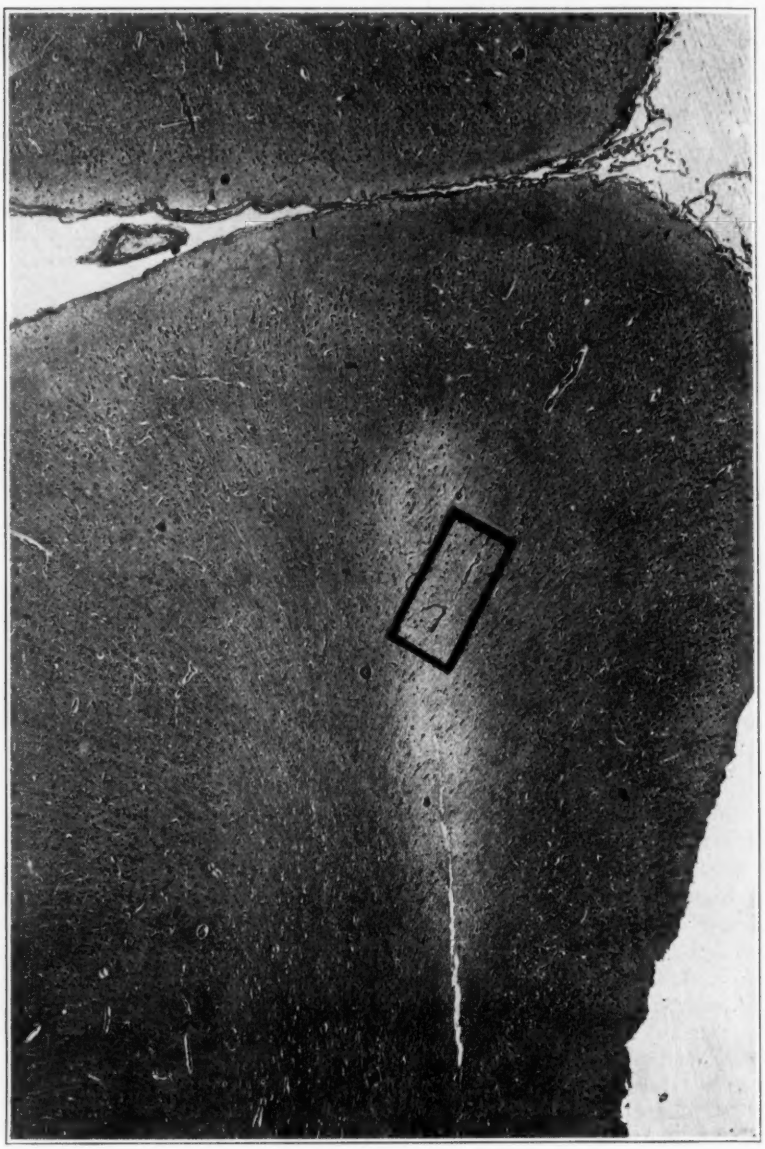

Fig. 3 (dog 3).—Parietal cortex. Note the well defined area of diffuse poor staining with preservation of cellular elements. Bodian's silver method; × 43.

Histologically unstained sections, cut somewhat thicker than those studied with various staining methods, showed practically no trace of trypan blue under the microscope. Occasionally, pyknotic nerve cells appeared to be evenly, but lightly, stained throughout. This was true despite the fact that an adequate amount of

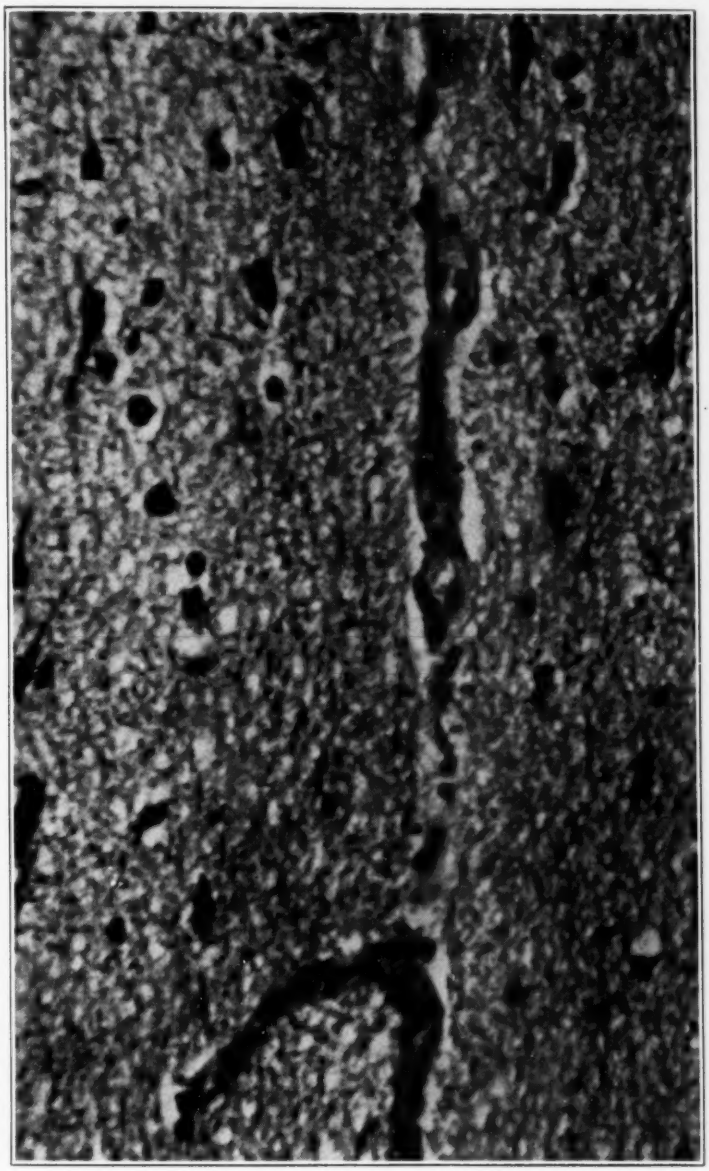

Fig. 4 (dog 3).—Higher magnification of the blocked area in figure 3, showing an intact vessel, absence of hemorrhage and general preservation of formed tissue elements. × 120.

dye had been given a sufficiently long time before death to permit microscopically visible staining to take place in body organs, such as the epithelium of convoluted tubules in the kidneys, the Kupffer cells in the liver and the reticuloendothelial cells of the lymph nodes.

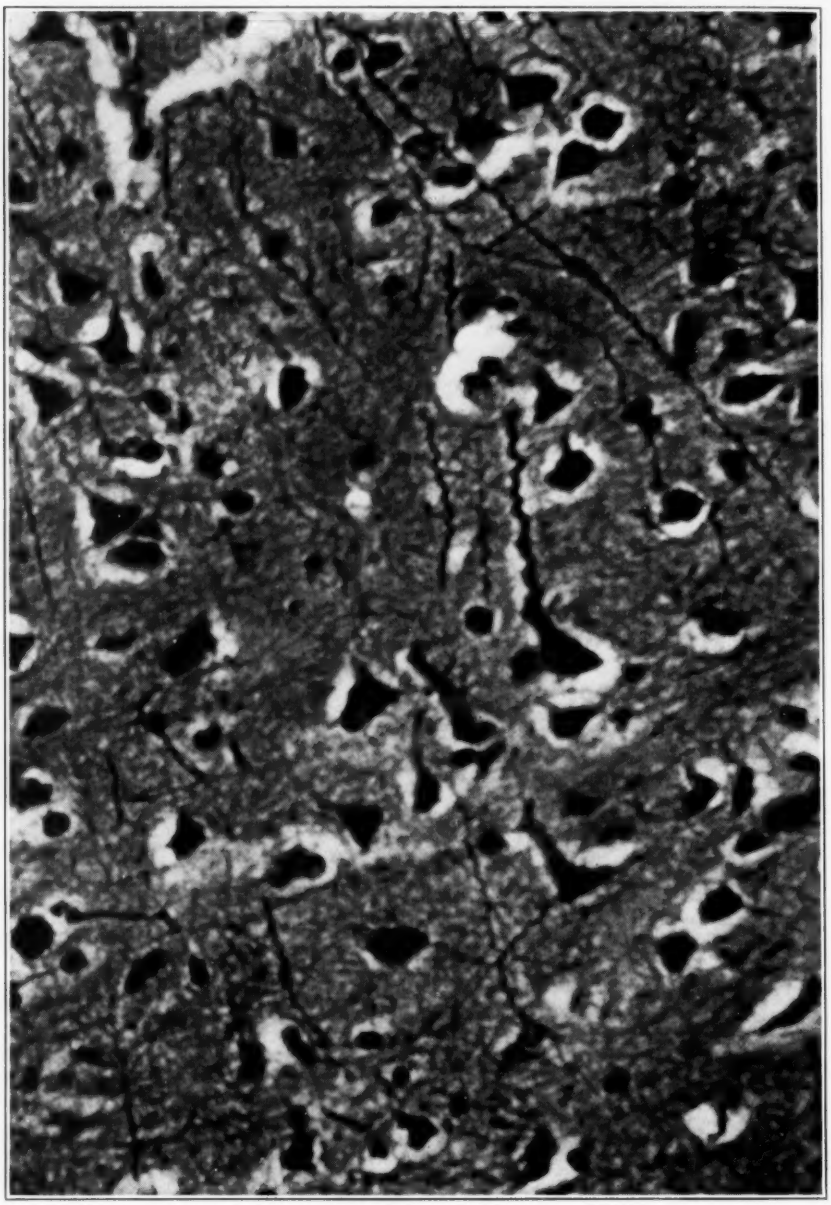

Fig. 5 (dog 11).—Frontal cortex. Note the marked damage to nerve cells with intact ground substance. This area was not vitally stained (see text). Bodian's silver method; × 120.

In at least 1 instance gross examination revealed a localized blue tinge in the subcortical white matter, with no recognizable cortical lesion in the vicinity. Microscopically, the nerve cells in the adjoining cortex appeared moderately shrunken, stained homogeneously with hematoxylin and eosin and showed, especially in silver sections, marked corkscrewing of the apical dendrites. The surrounding ground substance in these areas, however, appeared entirely normal and took all stains well, in conformance with the gross appearance and lack of vital staining, thus indicating damage only of the nerve cells, secondary to the lesion in the white matter, in contrast to the striking loss of ground substance, with occasionally almost undisturbed cytoarchitecture, characteristic of all primary cortical lesions produced by transient air embolization.

The striking feature in all cases was the apparently absolute correlation of gross vital stainability of the cortical ground substance and its loss of microscopic stainability in sections following pathologic alteration by transient ischemia. By means of these staining characteristics, a fairly distinct boundary was drawn between normal and altered tissue, which appeared to disregard completely all cytoarchitectural and other local peculiarities of the formed elements in the affected areas, and to be dependent entirely on the condition of the ground substance.

In every case in which operation was successfully performed, clinical observation revealed signs of decerebration, varying in degree, which developed gradually after operation and gradually receded to some extent, leaving various minor, focal neurologic lesions. In only 1 animal was there definite evidence of reaction of the central nervous system to the injection of the dye, once about twenty-four hours after operation (first injection; 11 cc. of 1 per cent trypan blue), and again about twenty-eight hours after operation (third injection; 12 cc.). In each instance irregular muscular twitchings of the right foreleg and shoulder, which had been observed throughout the preceding (postoperative) night, in the same form and involving the same muscle groups, recurred immediately after the injection, increased slightly in intensity for the next ten minutes and then decreased and disappeared. There was no evidence of any reaction implying a toxic effect on areas of the brain other than those already involved by the operative procedure and neurologically indicated before the injection of dye. These observations seem to corroborate the morphologic impression that the dye does not penetrate the brain tissue beyond the area of tissue alteration, despite the absence of any intervening barrier of endothelial cells or other formed elements.

SUMMARY AND CONCLUSIONS

The two chief hypotheses concerned with the nature of the blood-brain barrier are presented, and reference is made to the use of vital staining in the study of this phenomenon.

Controlled experiments with cerebral air embolization and subsequent intravenous administration of trypan blue are reported, and the gross and microscopic observations are described.

The microscopic changes were: exquisitely focal, chiefly intracortical, areas showing varying degrees of loss of stainability in sections. The general appearance of these lesions in stained sections appeared to be due primarily to definite changes in the intercellular ground substance, with occasionally no decrease in the number of cellular elements but with

always some degree of acute ischemic damage to the nerve cells. Blood vessels, on the other hand, appeared intact in almost every instance, showing only some endothelial hypertrophy and occasional hemorrhages in the larger lesions. All lesions were sharply demarcated from normal adjoining tissue and appeared to be entirely independent of cortical lamination or other regional peculiarities of the formed elements.

All lesions, apparently, stained grossly with trypan blue, regardless of the presence or absence of histologically determinable damage to the blood vessels.

Despite the extravascular presence of the toxic dye, there was neither anatomic nor neurologic evidence of any invasion of or effect on normal brain tissue adjoining areas damaged by embolization.

These observations are considered to be additional evidence that the peculiar behavior of the nerve structures toward intravascular trypan blue is an expression not of the special retentive powers of the cerebral capillary endothelium but of the peculiar constitution of the intact cerebral tissues, in accordance with King's hypothesis. Moreover, it would appear that the amorphic, colloidal ground substance which constitutes the bulk of the cerebral cortex represents the essential factor in which this peculiarity resides.

CONVULSIONS ASSOCIATED WITH TUMORS OF THE CEREBELLUM

CLINICAL AND PATHOPHYSIOLOGIC FEATURES

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It is generally thought that fits are not of usual occurrence in cases of tumors of the cerebellum. It is further agreed that when such episodes do occur the fit is of a tonic opisthotonic character. It is believed that this convulsive pattern indicates a crisis in the progress of the disease, which suggests the presence of a tumor of the cerebellum. Further, as a rule of thumb clinical tenet, it is generally accepted that convulsions of other than the tonic type do not occur in the presence of these tumors (Stewart,[1] Bailey,[2] Cushing,[3] Jelliffe and White,[4] Wechsler [5]).

A survey of 158 cases of verified intracerebellar tumors in patients presenting themselves for treatment at the Hospital of the University of Pennsylvania shows evidence contrary to the general clinical agreement on this subject. Findings in this survey indicate that the incidence of convulsions is apparently higher than is generally believed; that the convulsions do not conform to a type pattern, since every possible variety of fit was observed, and that the convulsions may occur not only as a terminal crisis but at any time in the progress of the disease.

In the survey, every attempt has been made to rule out any case in which there was a history of convulsions prior to the onset of the tumor symptoms. Likewise, instances of metastatic tumor or seeding medulloblastoma have not been included. The facts that the convulsions

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From the Department of Neurosurgery, Hospital of the University of Pennsylvania.

1. Stewart, P.: The Diagnosis of Nervous Diseases, London, Edward Arnold & Co., 1908.

2. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

3. Cushing, H.: Experiences with the Cerebellar Medulloblastoma, Acta path. et microbiol. Scandinav. **7**:1, 1930.

4. Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1915.

5. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 2, Phladelphia, W. B. Saunders Company, 1931.

recorded are the result of observations by numerous persons; that the descriptions are many times inadequate, and that secondary underlying disease processes are a constant possibility must be weighed in a true evaluation of the findings. Even in view of these considerations, the result of the survey appeared to be unusual and contrary to general opinion and statements in textbooks. This conclusion seemed to warrant reference to previous literature to determine whether the findings were unusual.

HISTORICAL SURVEY

The observation of convulsions in a case of tumor of the cerebellum was apparently first recorded in 1691 by Wurffbain.[6] This author described the state in a child aged 2 years:

> . . . the neck was bent in the form of a bow and, being drawn backward onto the back with great violence and resting on the shoulder blades, there stuck while the unhappy infant kept screaming . . . the symptoms being identical with that type of convulsion traditionally styled opisthotomy.

Hughlings Jackson's[7] report followed in 1871. The clinical concept which he presented identified the tonic or "cerebellar" fit as a "lowest level fit" and described it as a "tetanus-like seizure." Jackson reported the case of a child aged 5 years with a tumor of the cerebellum whose convulsions were observed and described by Sir Stephen Mackenzie, as follows:[7]

> Sometimes, but not always, the seizure was preceded by a loud cry. There was no marked twitching of the face nor any special deviation of the eyeballs. His hands were clenched; his forearms were flexed on the upper arms, which were generally kept to the sides. The head was drawn back and the back was curved. His legs were always extended to the fullest possible degree, the feet being arched backward. Sometimes he passed urine and feces in the attack. The seizures generally lasted about 3 or 4 minutes and, when passing off, they returned if he were moved about.

Mackenzie included the accompanying sketch of the patient with this description.

Neurologic literature concurs in this conception of the "cerebellar fit." Later authors have accepted it as characteristic of the convulsive state associated with cerebellar tumors. Grinker, Wechsler, Jelliffe and White and others have made brief mention of the occurrence, and some have presented a description of such similarity to that of Jackson as to make further quotation unnecessary.

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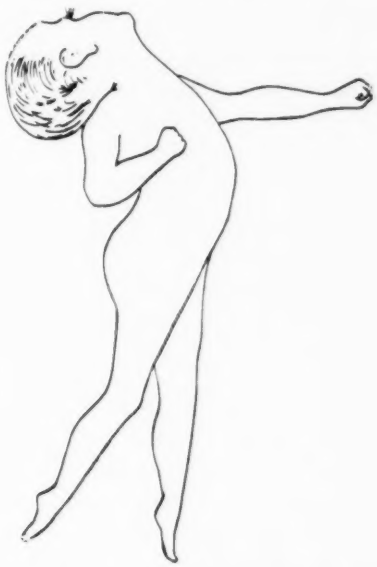
6. Wurffbain, J. P.: Hydrocephalo interno cum violentissima capitis tergum versus retractione convulsiva, translated by J. F. Fulton, J. Nerv. & Ment. Dis. **70**:577, 1929.

7. Jackson, J. H.: Case of Tumor of the Middle Lobe of the Cerebellum: Cerebellar Paralysis with Rigidity—Occasional Tetanus-Like Seizures, Brain **29**: 425, 1906.

8. Footnote deleted on proof.

That convulsions which do not follow this pattern occur in cases of tumors of the cerebellum is recognized in the literature. This fact was particularly commented on by Collier,[9] in 1904. He devoted one section of his paper to "The Occurrence of Jacksonian Epilepsy, Hemi-Epilepsy and General Convulsion in Connection with Tumors of the Brain Stem and Cerebellum." He reported 2 cases in which the patients were repeatedly observed to have had local convulsions of slow spread confined to the arm and face. Hemiepilepsy was observed to occur in 1 case of glioma of the pons and in 1 of cerebellar tumor. Several generalized convulsions occurred in cases of tumor of the brain stem and



Tetanus-like seizures in a case of tumor of the middle lobe of the cerebellum.

cerebellum. These convulsions were of the "cortical" type, to be distinguished from the "lowest level fit" of Jackson. Collier concluded that "the occurrence of local convulsions of hemiepilepsy and of general convulsion when presenting for the first time, long after the general signs of intracranial growth have appeared, is to be disregarded as a localizing sign." Other writers who have made similar observations include Jackson, who noted that, in addition to the typical tonic seizure, there is in some cases of cerebellar disease "only a fragment of the tetanus-like condition." Jackson recorded also cases reported by Dresch-

9. Collier, J.: False Localizing Signs of Intracranial Tumor, Brain **27:** 410, 1904.

feld and by Drummond [10] in 1880. In the former's case the patient had a tonic fit, "followed by slight clonic contractions of very short duration." In the latter's case the patient had a tonic attack; then, "for 3 to 4 minutes, clonic spasms of the right arm and leg ensued."

Stewart and Holmes,[11] in 1904, recorded the symptoms in a study of 40 cases of cerebellar tumors, in 22 of which autopsy was performed. Particular attention was given to a case of extracerebellar tumor with autopsy, in which there was "a long series of seizures of a peculiar nature —they preceded the vertigo and consisted of an isolated jerk or short series of jerks of sudden shock-like character of any part of the homolateral arm lasting over a period of 2-3 minutes. The movements were irregular in distribution and sequence and according to the patient, occasionally affected the contralateral arm simultaneously but always to a slighter degree." In this group of cases reported with autopsies 1 patient had fainting spells; another had twitching of the face, and a fourth had convulsions which were not described.

Oppenheim [12] stated that ipsilateral convulsions in cerebellar disease seem to occur exclusively with neoplasms and that rhythmic convulsions of the muscles of swallowing and of the larynx observed in disease of the posterior fossa may be caused by distant or neighborhood effects. Stewart, cited by Grinker,[13] pointed out that "epileptiform fits, cerebral in type, may occur in cerebellar tumors due to the general increase of intracranial pressure."

Reports of cases to substantiate these opinions do not appear in the literature. Only brief reports of the convulsive state in cases of tumor of the cerebellum may be found. Keschner and Grossman [14] reported 3 instances among 29 patients with intracerebellar tumors. One patient had two attacks of rigidity which involved the entire body. One had several generalized convulsions. A third had tonic and clonic convulsions. Cushing,[15] in a report of 76 cases of astrocytoma of the cerebellum, briefly summarized the histories in 20 cases. Eight of this group of 20 patients had seizures. Two of these had fainting attacks; 1 had a succession of jacksonian seizures, and the remaining 5 had tonic convulsions. In Cushing's series of medulloblastomas, summaries

10. Dreschfeld, cited by Jackson.[7] Drummond, cited by Jackson.[7]

11. Stewart, T. G., and Holmes, G.: Forty Cases of Cerebellar Tumor, Brain **27**:522, 1904.

12. Oppenheim, H.: Textbook of Nervous Diseases, ed. 7, Berlin, S. Karger, 1923.

13. Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

14. Keschner, M., and Grossman, M.: Cerebellar Symptomatology: Evaluation on Basis of the Intracerebellar and Extracerebellar Lesions, Arch. Neurol. & Psychiat. **19**:78 (Jan.) 1928.

15. Cushing, H.: Experiences with Cerebellar Astrocytomas, Surg., Gynec. & Obst. **52**:129, 1931.

of only 4 cases are presented. In 2 of these convulsions were stated as being present. They were tonic in nature.

A survey of the literature seems to indicate that convulsions not infrequently occur in cases of tumor of the cerebellum; that the tonic "cerebellar fit" is the general pattern of the convulsion; that variations of this pattern occur, and that these variations may assume the quality of the "cortical" type of convulsion.

MATERIAL AND CASES

Of 158 cases of verified intracerebellar tumors, convulsions were present in 21 and syncopal attacks in 13, making a total of 34 instances of the convulsive state, or an incidence of 21.5 per cent. In 13 of the 19 cases in which the patient died, autopsy was performed.

Syncopal Attacks.—Syncopal attacks were frequent. Their occurrence was predominantly in the early and middle periods of the disease. There were 13 patients in the group with these attacks. A typical instance follows:

E. B., a woman aged 25, on her admission to the hospital in April 1925, complained of pain in the right ear, headache, unsteadiness of gait and numbness

TABLE 1.—*Convulsive State in 158 Cases of Intracerebellar Tumor*

Type	No. of Cases	No. of Deaths	No. of Autopsies
Segmental-clonic	7	5	3
Generalized			
Clonic	3	3	3
Tonic	11	6	4
Syncopal	13	5	3

of the right side of the face. Symptoms were first noticed in October 1923, when she experienced pain in the back of the head and in the neck. In February she noticed difficulty in walking and impairment of vision in the right eye. In March the unsteadiness of the gait increased. She had twitching of the muscles of the right side of the face and of the lips. During this month, also, she had attacks of fainting, which occurred four to five times a day. During the attacks, which lasted about a minute, she was unconscious and became cyanotic. Recovery was rapid, with profuse perspiration.

Neurologic examination showed the patient to be generally hypotonic. Three diopters of papilledema was present in the right eye and 2 in the left. Incoordination could not be demonstrated in the extremities, although the patient tended to fall to the right in tests for gait. Horizontal nystagmus was present on lateral gaze; the right side of the face was weak. At operation a cyst in the right hemisphere was evacuated. The patient died shortly after operation.

Data on attacks occurring in the members of this group are indicated in table 2.

Segmental-Clonic Convulsions.—Seven patients presented one or more attacks of the segmental clonic type of convulsion at some time during the course of their disease. A typical account of one member of this group follows:

G. S., a man aged 38, a carpenter, was well until December 1930, when he began to vomit. In April 1931 headache followed attacks of vertigo. At this time

also the patient began to have spells of shaking in both upper extremities. Tremor was rapid and coarse, the spells occurring every two days. Examination in the following month showed that the patient was dull and that he held his head in pain. He was unable to stand erect because of weakness of the lower extremities. There was moderate hypotonia of the left upper extremity; finger to nose tests showed slight ataxia and dysmetria of the right upper extremity; rapidly alternating movements were impaired in both hands. The patient was unable to raise

TABLE 2.—*Data on Patients with Syncopal Attacks Accompanying Cerebellar Tumor*

Sex; Age, Yr.	Character of Attacks	Position of Cerebellar Tumor	Type of Tumor	Degree of Choking of Disks	Stage of Disease in Which Attacks Occurred	Result
M 11	Two fainting spells	Right lobe	Astrocytoma	Papilledema	Middle	Operation; death
F 25	Four to five fainting attacks daily	Right lobe	Glioma	2-3 D.	Late	Operation; death
M 26	Unconsciousness for 10-15 min.	Left of midline	Meningioma	6 D.	Early	Operation; patient lived
F 17	Fainting on two occasions	Right lobe	Astrocytoma	4 D.	Early	Operation; patient lived
M 7	Fainting on one occasion	Left lobe	Astroblastoma	2-3 D.	Early	Operation; patient lived
M 30	A number of syncopal attacks	Midline	Medulloblastoma	Haziness	Early	Operation; autopsy
M 31	Unconsciousness for 10 min.	Left lobe	Astrocytoma	3-4 D.	Early	Operation; autopsy
F 39	A number of brief syncopal attacks	Left lobe	Astrocytoma	Haziness	Middle	Operation; patient lived
F 10	Unconsciousness for 20 min.	Right lobe	Astrocytoma	4-5 D.	Late	Operation; patient lived
F 28	Attacks of fainting	Midline	Hemangioma	4 D.	Early	Operation; patient lived
M 39	Attacks of syncope at onset of illness	Right lobe	Meningioma	.....	Early	Autopsy
M 11	Had fainting spell with abortive rigid convulsion	Left lobe	Cyst	4-5 D.	Late	Operation; patient lived
F 33	Syncopal attack following vomiting	Right lobe	Cyst	.....	Late	Operation; patient lived

himself from the dorsal decubitus position without use of the arms. Reflexes in the lower extremities were pendulous. Papilledema of 2 D. was present. There was no nystagmus. While being examined the patient had "mild, fairly rapid, pseudoclonic jerkings of the muscles of the shoulder girdle, arm and forearm, lasting for thirty seconds. There was no characteristic type or distribution of the clonic contractions. They were not of the usual flexor type seen in cases of cortical irritation, and they caused no regular pattern of movement of the extremities. Palpation of the muscles during the attack indicated that the contraction was a clonic convulsion rather than tremor." Routine studies gave normal results. A ventriculogram was recommended to localize the lesion.

Colonic irrigation was given for relief of constipation, an enema being considered unwise in view of the fact that the localization of the tumor was unknown. After an hour of irrigation the patient was described as presenting the picture of shock. At this time Dr. Charles H. Frazier saw him have a "definite clonic convulsion in the upper extremities." He died twelve hours after ventricular trephine. Autopsy showed pronounced hydrocephalus, with a pressure cone and a right cerebellar cyst. Table 3 presents data concerning the members of this group.

TABLE 3.—*Data on Patients with Segmental Convulsions, Clonic Type, Accompanying Cerebellar Tumor*

Sex; Age, Yr.	Parts Involved	Position of Cerebellar Tumor	Type of Tumor	Degree of Choking of Disks	Stage of Disease in Which Convulsion Occurred	Result
F 3	Three attacks of convulsions of left arm and leg, associated with violent grimaces and gritting of teeth, while in ward	Midline	Medulloblastoma	Marked	Late	Operation; death
M 5	Clonic involuntary convulsions in right arm	Right lobe	Tuberculoma	5-6 D.	Early	Operation; death
F 14	Four attacks of spasms of facial muscles; two on right side, two on left	Midline	Astrocytoma	4-5 D.	Early	Operation; patient lived
M 38	Case reported in detail	Right lobe	Cyst	2 D.	Middle and terminal	Autopsy
F 51	Convulsions of left side of face, lasting for several minutes; stiffening of whole body with unconsciousness on several occasions	Left lobe	Meningioma	5 D.	Middle	Operation; patient living
F 14	Four attacks of convulsions of right side, associated with incontinence	Midline	Medulloblastoma	3-4 D.	Early	Operation; autopsy
F 33	Clonic convulsions of right upper extremity; four attacks before admission, then one daily	Right lobe	Astrocytoma	Doubtful on right side, early on left	Middle	Operation; autopsy

Clonic Convulsions.—In this group there were 3 instances of generalized convulsions of the clonic type; in 2 the convulsions occurred terminally. Two of the cases are reviewed briefly.

J. W., a farmer aged 48, was well until nine months before admission. At this time vision became impaired, the impairment progressing to total blindness. Attacks of vomiting, associated with frontal headaches, were complained of. Eight months previously convulsions had taken place. The patient had six or seven seizures daily. The convulsions were generalized, not affecting one side of the body more than the other. During the spells the patient put his thumbs between the middle and the index fingers, and his entire body shook. During these episodes he was unconscious and frothed at the mouth. Examination showed confusion, poor memory and visual and auditory hallucinations; 5 D. of papilledema, with postpapillitic atrophy, was present in each eye. Horizontal nystagmus was present

on both right and left lateral gaze. Bilateral palsy of the sixth nerve and incoordination in the right hand were noted. A roentgenographic survey showed no abnormalities. The cerebrospinal fluid pressure was 250 mm. of water. Ventriculographic study disclosed a tumor in the posterior fossa, occluding the fourth ventricle and the aqueduct of Sylvius. The patient died after a second operation, four years after the first. At autopsy a hemangioma was observed in the right hemisphere.

E. B., a girl aged 19, had headache, loss of vision and difficulty in walking of eight months' duration. She was apathetic. Station was unsteady, with a positive Romberg sign. Coordinated movements were poorly performed in both upper extremities. Nystagmus was elicited on lateral gaze. Papilledema with optic atrophy was present bilaterally. Roentgen examination of the head indicated a perforation of the occipital bone just below the external occipital protuberance. Shortly after admission the patient was observed to have the first convulsion. Three days later the second convulsion took place, and the following day, while the patient was being prepared for operation, the third generalized clonic convul-

TABLE 4.—*Data on Patients with Generalized Convulsions, Clonic Type, Accompanying Cerebellar Tumor*

Sex; Age, Yr.	Character of Convulsions	Position of Tumor	Type of Tumor	Degree of Choking of Disks	Stage of Disease in Which Convulsions Occurred	Outcome
M 48	Reported in detail	Right lobe	Hemangioma	5 D.	Early	Operation; autopsy
F 33	Series of generalized clonic convulsions occurring every 3-4 minutes	Right lobe	Astrocytoma	Early on right side, doubtful on left	Terminal	Operation; autopsy
F 19	Reported in detail	Between hemispheres	Dermoid cyst	6 D. in both disks	Late	Autopsy

sion occurred, lasting two minutes. After this the patient died. At autopsy a dermoid cyst located between the hemispheres was disclosed.

Tonic and Doubtful Types of Convulsions.—There were 12 instances of convulsions of the tonic and doubtful types. Noteworthy is the variation in the pattern of the convulsions in the members of this group. The typical "cerebellar fit" was distinguished by its infrequency. Fragments of the tonic convulsion appeared in a number of cases. One instance illustrating the atypical character of the tonic convulsion follows.

L. L., a woman aged 32, had excessive headache and vomiting in her third month of pregnancy. She had been well until January, when there developed what seemed to be the usual nausea and vomiting of pregnancy. Early in February these symptoms became so severe as to force the patient to go to bed. In the middle of this month the patient was admitted to an obstetric service of the hospital. Early in March the intense headaches became associated with mental confusion. Marked bilateral papilledema was noted in the presence of normal renal function. At this time the patient had a convulsion which was seen only by a nurse and was reported as "hysterical." This episode was marked by generalized rigidity, which lasted only a few minutes, and was associated with semiconsciousness. Seven days later the patient had another tonic convulsion lasting three minutes, with unconsciousness lasting thirty to forty-five minutes. During this episode she frothed

at the mouth and was rigid. Dr. William G. Spiller made the diagnosis of toxemia of pregnancy. Lumbar puncture showed a pressure of 70 mm. of mercury. A ventricular estimation and ventriculogram were made, followed by suboccipital

TABLE 5.—*Data on Patients with Generalized Convulsions, Tonic Type, Accompanying Cerebellar Tumor*

Sex; Age, Yr.	Character of Convulsions	Position of Tumor	Type of Tumor	Degree of Choking of Disks	Stage of Disease in Which Convulsions Occurred	Result
M 15	Series of generalized convulsions with rigidity and contraction of extremities and to and fro movements of head; each lasting 2-3 min., series lasted 1½ hr.	Left lobe	Glioma	Bilateral	Early	Operation; death
F 13	Numerous generalized convulsions at home, two in hospital; body in extension; upper extremities went through athetoid movements; head moved to and fro; attack lasted 30 min.	Midline	Meningioma	Blind	Late	Operation; autopsy
M 40	Two convulsions within hour, marked by generalized rigidity, with twitching of left upper extremity; cessation of breathing	Left lobe	Sarcoma	3 D.	Terminal	Autopsy
M 40	Attacks of unconsciousness with generalized rigidity, occurring 2-3 times an hour if disturbed	Right and left lobes	Sarcoma	5 D.	Middle	Autopsy
M 39	Attacks of involuntary retraction of head, gradually becoming more severe	Left lobe	Cystic glioma	4 D.	Middle	Operation; patient lived
M 5	Generalized convulsion, following which patient could not walk or see well	Midline	Medullo-blastoma	Blind	Early	Operation; patient lived
F 32	Reported in detail	Midline	Cyst	4 D.	Middle	Operation; death
M 13	Two generalized convulsions lasting 1 min.	Left lobe	Medullo-blastoma	None	Late	Operation; patient lived
F 51	Attacks of generalized stiffening of entire body with unconsciousness	Left lobe	Meningioma	3-4 D.	Middle	Operation; patient lived
M 6	Five generalized convulsive seizures during which the body stiffened, as did the extremities, lasting 3-4 min.	Midline	Dermoid cyst	4-5 D.	Early and middle	Operation; patient lived
M 7	Intermittent tremors of all extremities followed by generalized tonic convulsion and embarrassed respirations	Midline	Astrocytoma	1 D.	Terminal	Autopsy

craniectomy. The exploration revealed a cystic tumor of the vermis, the microscopic diagnosis being that of spongioblastoma unipolare. The patient died three days later. No autopsy was done. This group of cases is tabulated in table 5.

A review of the material in summary shows that of the 34 patients having convulsions or syncopal attacks 18 were males and 16 females.

The ages ranged from 3 to 51. In 11 instances the lesion was located in the midline; in 11 instances, also, the right, and in 11 the left, lobe was the site of the tumor. In 1 instance the growth was reported as invading both hemispheres. In 5 cases there was moderate elevation of the optic disks; in 26, advanced papilledema, and in 1, no choking of the disks. In 2 cases papilledema was not mentioned. Convulsions occurred in the early part of the illness in 14 cases, in the middle in 8 cases and late in 12 cases. In 7 of the 13 cases of syncopal attacks the episodes appeared early, thus making higher the total for the group with early occurrence. Nineteen of the patients died, 6 prior to operation. Autopsy was performed in 13 cases.

PATHOPHYSIOLOGY AND PATHOGENESIS

Study of the material shows that a variety of types of convulsions occurred in patients with cerebellar tumors. These ranged from syncopal attacks, which are considered at one end of the "convulsive spectrum," to tonic fits, at the other. As previously mentioned, attention has been focused largely on the tonic "cerebellar fit," and several explanations have been offered to explain its pathophysiolgic features. It is evident, however, that the other varieties of convulsive seizures also demand an explanation. Furthermore, it is reasonable to suspect that a common mechanism accounts for the various convulsive manifestations. Evidence will be adduced to show that this is the case.

Since those who have written on cerebellar symptomatology have been mainly concerned with the pathogenesis of the tonic cerebellar fit, it is of interest to review the explanations offered, particularly in view of modern neurophysiologic knowledge.

General Considerations.—Since the teachings of Jackson, it has been generally accepted as a clinical tenet and as a physiologic fact that the clonic component of the convulsive attack, or more generally the clonic convulsion, arises from discharges originating in the motor cortex. The basis for this belief grew from observations on epileptic persons, from observations of clonic movements in the presence of cortical lesions and from the experimental observations of numerous physiologists that electrical stimulation of the motor cortex gave rise to phasic movements of the opposite extremities. On the other hand, the tonic component, or tonic fit, was assumed to arise through release of the lower postural centers from cortical control. The phenomenon of decerebrate rigidity, discovered by Sherrington,[16] gave experimental demonstration of the fact that tonic extensor patterns occurred when the lower postural mechanisms were released from the influence of the cortex by appropriate section through the brain stem.

16. Sherrington, C. S.: Decerebrate Rigidity and Reflex Coordination of Movements, J. Physiol. **22**:319, 1898.

It is now apparent, however, that the functional organization of the motor system is too complicated to be explained altogether in such a simple and categorical fashion. The mechanisms responsible for the tonic and clonic elements of the convulsion can no longer be rigidly localized. Pike and Elsberg;[17] Pike, Elsberg, McCulloch and Chappell,[18] and Ward and Clark,[19] among others, established that clonic convulsions may be produced in animals deprived of their motor cortex if time is given for them to recover from the effects of the operation. It is clear from their work that a large degree of compensation exists within the nervous system and that the clonic component of the convulsion may, under certain circumstances, be produced by extrapyramidal mechanisms. Pike, Elsberg and their associates summed up their views as follows:

> It does not seem probable that when the motor system is intact, one part of the mechanism gives rise to movements of one type and another part to movements of another type.

They admitted, however, that in the intact organism the motor cortex is responsible for the clonic component. The question of mechanisms responsible for various kinds of movements has been further complicated, at least in so far as clinical interpretation is concerned, by modern studies on the electrical excitability of the extrapyramidal cortical areas. Foerster,[20] Fulton[21] and Penfield and Boldrey,[22] among others, established that stimulation of areas 6a and 5 gives rise to movements which may still be obtained after removal of the motor cortex. The studies of Brown[23] and Ingram, Ranson and others[24] demonstrated that certain

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17. Pike, F. H., and Elsberg, C.: Studies on Epilepsy: II. The Occurrence of Clonic Convulsive Seizures in Animals Deprived of the Cerebral Motor Cortex, Am. J. Physiol. **22**:337, 1925.

18. Pike, F. H.; Elsberg, C.; McCulloch, W. S., and Chappell, M. N.: The Problem of Localization in Experimentally Induced Convulsions, Arch. Neurol. & Psychiat. **23**:847 (May) 1930.

19. Ward, J. W., and Clark, S. L.: Convulsions Produced by Electrical Stimulation of the Cerebral Cortex in Unanesthetized Cats, Arch. Neurol. & Psychiat. **39**:1213 (June) 1938.

20. Foerster, O.: The Motor Cortex in Man in the Light of Hughlings Jackson's Doctrines, Brain **59**:135, 1936.

21. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

22. Penfield, W. C., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**:389, 1937.

23. Brown, T. G.: Note on the Physiology of the Basal Ganglia and Mid-Brain of the Anthropoid Ape, Especially in Reference to the Act of Laughter, J. Physiol. **49**:185, 1915.

24. Ingram, W. R.; Ranson, S. W.; Hannett, F.; Zeiss, F. R., and Terwilliger, E. H.: Results of Stimulation of the Tegmentum with the Horsley-Clark Stereotaxic Apparatus, Arch. Neurol. & Psychiat. **28**:513 (Sept.) 1932.

types of movements may be obtained from stimulation of the brain stem, and Sachs and Fincher [25] and Denny-Brown, Eccles and Liddell [26] elicited crude movements from stimulation of the cerebellar nuclei.

Even this brief survey indicates the complexity of the factors involved in providing an explanation for the so-called cerebellar fit, as well as for the other types of convulsive phenomena seen in association with cerebellar tumors. In a sense, the problem here is similar to that encountered in attempting to explain, on physiologic grounds, the manifold motor patterns met in epilepsy and in cortical and subcortical disease.

In cases both of cerebellar tumors and of epilepsy a tonic or tetanic spasm may precede the clonic attack or may comprise the entire fit.

Physiologic analysis suggests that the various types of convulsive phenomena occurring in association with cerebellar tumors are due to remote effects on the cortex of disturbances in the cerebral blood flow resulting from increased intracranial pressure. Since most attention has been centered on the "cerebellar fit" and since the entire problem, in a sense, revolves about the explanation for this special phenomenon, it is of considerable interest to review and analyze the explanations that have previously been offered. For the sake of completeness, certain other explanations not before touched on are mentioned in passing.

1. *Physiologic Decerebration.*—A number of authors, including Bailey and Fulton, have expressed belief that the tonic spasm with extension of the extremities and opisthotonos occurring in the presence of a cerebellar tumor represents temporary physiologic decerebration. This opinion seems to be based largely on the resemblance to decerebrate postures in lower animals produced by transections of the brain stem and the resemblance to the attitudes seen in a few cases in man in which the brain stem has presumably been transected by a tumor, as in the cases of Walshe [27] and of Davis.[28] Yet the way in which this is accomplished by a tumor of the cerebellum is not clearly explained. There seems to be no obvious way in which a cerebellar tumor could compress the brain stem above the level of the vestibular nuclei so as to produce physiologic transection. This might conceivably be possible anatomically with a midline lesion involving the upper portion of the vermis, but in a number of cases in the series presented the tumor was in one of the cerebellar hemispheres. A theoretic possibility is compression of the

25. Sachs, E., and Fincher, E. F.: Anatomical and Physiological Observations on Lesions in the Cerebellar Nuclei in Macacus Rhesus, Brain **50**:350, 1927.

26. Denny-Brown, D.; Eccles, D., and Liddell, E. T.: Observations on Electrical Stimulation of the Cerebellar Cortex, Proc. Roy. Soc., London, s.B **104**: 518, 1929.

27. Walshe, F. M. R.: A Case of Complete Decerebrate Rigidity in Man, Lancet **2**:645, 1923.

28. Davis, L. E.: Decerebrate Rigidity in Man, Arch. Neurol. & Psychiat. **13**: 569 (May) 1925.

basilar artery against the clivus, with resulting ischemia of the brain stem and the pattern of decerebration. This would simulate the experimental decerebration produced by Pollock and Davis [29] by ligation of the basilar artery. However, it seems unlikely that either of these mechanisms operate, since it is hardly conceivable that an insult to the brain stem of such magnitude as to produce physiologic transection could be recovered from without profound evidences of injury to the brain stem, if survival could occur at all.

On the other hand, in a review of the cases of tumors of the midbrain and pons, in which there is actually the nearest approach to anatomic discontinuity of the brain stem, decerebrate and tonic fits have been found to be conspicuously absent. In 10 cases of mesencephalic glioma reported by Alpers and Yaskin [30] and in 11 cases of pontile tumor reported by Alpers and Watts [31] tonic fits were not observed, although in a number of these cases the brain stem was almost completely destroyed. However, in a number of these cases, as well as in the cases of pontile tumor reported by Needles,[32] there were generalized convulsions.

Wilson [33] reported a heterogeneous group of cases which were, in his opinion, examples of decerebrate rigidity occurring in man. The only feature which these cases had in common was the occurrence of tonic fits and extensor attitudes. The underlying diseases varied widely. In 1 case the process was a mesencephalic glioma; in several, intraventricular hemorrhage; in 1, meningitis, and in 1, purulent ependymitis following rupture of an abscess into the ventricular system. It is well known, also, that conditions such as tuberculous or chronic purulent meningitis, subcortical encephalopathies or hydrocephalus due to atresia of the aqueduct may also give rise to so-called decerebrate attitudes without any demonstrable injury of the brain stem. Furthermore, widespread cortical destruction in man following asphyxiation from an anesthetic or temporary cessation of circulation during anesthesia may result in clinical patterns of so-called decerebration accompanied by tonic fits. Pathologic study of these cases reveals widespread necrosis of the cortex, so extensive that the effect is as though the cortex were "stripped off," leaving the brain stem intact. Courville; [34] Löwenberg, Waggoner and

29. Pollock, L. J., and Davis, L. E.: Studies in Decerebration: I. A Method of Decerebration, Arch. Neurol. & Psychiat. **10**:391 (Oct.) 1923.

30. Alpers, B. J., and Yaskin, J. C.: Gliomas of the Pons: Clinical and Pathologic Characteristics, Arch. Neurol. & Psychiat. **41**:435 (March) 1939.

31. Alpers, B. J., and Watts, J. W.: Mesencephalic Glioma: Clinical and Pathologic Analysis of Ten Cases, Arch. Neurol. & Psychiat. **34**:1250 (Dec.) 1935.

32. Needles, W.: Brain Stem Syndromes, J. Mt. Sinai Hosp. **5**:503, 1938.

33. Wilson, S. A. K.: On Decerebrate Rigidity in Man and the Occurrence of Tonic Fits, Brain **43**:220, 1920.

34. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129, 1936.

Zbinden;[35] O'Brien and Steegmann,[36] and Steegmann[37] all agreed that the brain stem in cases of asphyxiation during anesthesia show no significant damage.

The therapeutic production of convulsions in man by metrazol and insulin frequently occasions severe tonic fits associated with extensor attitudes. According to the best evidence available,[38] these agents act by reducing the oxidation of the cortex to the extent that for a time the subject is "metabolically decorticated."

It appears that all the aforementioned conditions have in common only widespread physiologic or morphologic decortication. Meningitis, hemorrhage, asphyxiation, temporary cessation of circulation and hydrocephalus all may act to cause either temporary or permanent diffuse injury to the cortex. In all these conditions, however, in which decortication is a common factor, tonic fits and extensor attitudes occur. In summing up the evidence, it appears that, owing to the higher organization of the motor system in man, the phenomena elicited by transection of the brain stem in lower animals, and even in primates, as demonstrated by Fulton,[21] may be reproduced in man by decortication alone. Even in the cat Bard and Rioch[39] have pointed out that the loss of cortical control is the most important factor in the production of decerebrate phenomena. In surgically decorticated cats or in those from which only the motor cortex has been removed extensor rigidity of all the extremities develops when the animals are freely suspended. The extremities also resist flexion. Doubtless, under unusual circumstances true transection of the brain stem occurs in man, but it is also evident that most of the cases reported in evidence of decerebration are really instances of decortication. It is questionable whether the two conditions are distinguishable in man. Unfortunately, no one has succeeded in decorticating primates, but in man the conditions in which widespread decortication may be presumed to be present are accompanied by motor patterns indistinguishable from the decerebrate patterns of monkeys, and apparently also of primates. When these factors are taken into account, it becomes clear that the "cerebellar fit" may be evidence of

35. Löwenberg, K.; Waggoner, R., and Zbinden, T.: Destruction of the Cerebral Cortex Following Nitrous Oxide-Oxygen Anesthesia, Ann. Surg. **104**: 801, 1936.

36. O'Brien, J. D., and Steegmann, A. T.: Severe Degeneration of the Brain Following Nitrous Oxide Anesthesia, Ann. Surg. **107**:486, 1938.

37. Steegmann, A. T.: Encephalopathy Following Anesthesia: Histologic Study of Four Cases, Arch. Neurol. & Psychiat. **41**:955 (May) 1939.

38. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

39. Bard, P., and Rioch, D. M.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

transitory decortication rather than of transitory decerebration. With this viewpoint, it is possible to relate all the convulsive phenomena occurring with cerebrellar tumors to a common mechanism, namely, transient interference with cortical activity. It is also possible to explain the pathogenesis of the various types of convulsions in terms of well known principles of intracranial physiology. Before doing this, there are other mechanisms which should be mentioned as possible explanations of the "cerebellar fit."

2. *Stimulation of the Brain Stem.*—Walshe,[40] in discussing the causation of so-called decerebrate rigidity in man, expressed disagreement with the conclusions of Wilson and ascribed the cause of tonic fits to disturbances in the circulation of the brain stem which directly excite the gray matter. He stated that these fits "are equivalent to stimulation experiments on the brain stem." This statement is open to the objection that stimulation of the tegmentum of the brain stem experimentally, as performed by Brown [41] and by Ingram, Ranson and their associates,[24] did not produce these types of motor patterns. Further, it has long been known that stimulation of the brain stem of a decerebrate preparation actually inhibits the rigidity. On the other hand, if the disturbance of circulation is presumed to result from compression of the medulla by the impaction of the cerebellar tonsils in the foraminal ring, there is the objection that injury of the medulla below the level of the vestibular nuclei results in a flaccid, and not in a decerebrate, spinal preparation.

3. *Acute Physiologic Decerebellation or Cerebellar Stimulation.*—The following possibilities are merely mentioned for completeness. Luciani [42] showed that in dogs after acute decerebellation periodic seizures of opisthotonos and tonic extensor patterns developed. According to Fulton and Daws,[43] the same pattern is seen in monkeys. The question arises whether acute physiologic decerebellation occurs with cerebellar tumors and whether this mechanism can account for the tonic seizures. That the presence of a tumor in this region could produce this condition seems unlikely. Such total physiologic decerebellation could be caused, it would seem, only by general vascular disturbance in the nature of ischemia. The anatomic course and distribution of the posterior inferior and superior cerebellar arteries make it improbable that the

40. Walshe, F. M. R.: The Decerebrate Rigidity of Sherrington in Man, Arch. Neurol. & Psychiat. **10**:1 (July) 1923.

41. Brown, T. G.: On the Effect of Artificial Stimulation of the Red Nucleus in the Anthropoid Ape, J. Physiol. **49**:184, 1915.

42. Luciani, L.: Il cervelletto. Nuovi studi di fisologia normale e patologica, Florence, successori Le Monnier, 1891, p. 120.

43. Fulton, J. F., and Daws, R. S.: The Cerebellum: Summary of Functional Localization, Yale J. Biol. & Med. **10**:89, 1937.

entire circulation of the cerebellum could be occluded, even transiently, by a tumor.

Some evidence has been presented by Sachs and Fincher;[25] Magoun, Hare and Ranson,[44] and Denny-Brown, Eccles and Liddell[26] that stimulation of the interior of the cerebellum, more particularly the dentate and roof nuclei, may give rise to certain types of postural movements and alterations in body posture. Most of these investigations have been made on decerebrate preparations, and it is not known, at least in primates, what the effects of stimulation are on an intact animal. Moreover, the movements elicited did not resemble those seen in tonic fits.

4. *Cerebral Ischemia Secondary to a Rise in Intracranial Pressure.*—It is clear that any theory offered to explain the occurrence of the tonic "cerebellar fit" must also explain the other varieties of convulsive states seen, as well as the syncopal attacks. The common factor existing in all the cases reported here was increased intracranial pressure. That tumors in the posterior fossa, owing to their strategic position at the "bottle neck" of the cerebrospinal fluid pathway—the aqueduct and the fourth ventricle—cause early and great increases in pressure is a long-established fact. In addition to this factor, the direct pressure of the tumor on the great venous sinuses may also increase the intracranial pressure by producing a rise in the intracranial venous pressure. The clinical picture of a cerebellar tumor may thus be due predominantly to the general effects, and these may even overshadow the evidences of cerebellar deficit. It is evident that the remote effects of increased pressure may occasion symptoms referable to disturbances of other portions of the brain. The general increase in the intracranial pressure in the presence of a cerebellar tumor affects all parts of the brain above the tentorium. This increase is not present to the same degree in cases of supratentorial tumors, for there the pressure may be localized because of the presence of unyielding dural septums. Further, it is well known that for all practical considerations the Monroe-Kellie doctrine is valid, i. e., an increase in any component of the intracranial contents necessitates diminution in other components.

Cushing,[45] many years ago, and after him, Eyster, Burrows and Essick[46] and Wolff and Forbes[47] showed experimentally that an increase

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44. Magoun, H. W.; Hare, W. H., and Ranson, S. W.: Electrical Stimulation of the Interior of the Cerebellum in the Monkey, Am. J. Physiol. **112**:329, 1935.

45. Cushing, H.: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Pressure, Am. J. M. Sc. **124**:375, 1902.

46. Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: Studies on Intracranial Pressure, J. Exper. Med. **11**:489, 1909.

47. Wolff, H. G., and Forbes, H. S.: Cerebral Circulation: V. Observations on the Pial Circulation During Changes in Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928.

in the intracranial pressure produced ischemia of the cortex when fluid was forced into the subarachnoid space. When only slight increases of pressure were produced the venous current was slowed, with an increase in the difference in oxygen content of arterial and of venous blood. When, according to Cushing, the intracranial pressure was raised to the level at which it exceeded the arterial blood pressure, the observed surface of the brain became pale and blanched and the capillaries invisible. This set into action the medullary vasomotor reflexes, which raised the blood pressure so that the intracranial pressure was overcome. The capillaries again filled, and the cortex received an adequate circulation. As the pressure was raised higher, the same cycle was repeated and the compensatory mechanisms operated to preserve the integrity of the cerebral circulation until a point was reached at which they could not longer function. Death then occurred. Cushing and Wolff and Forbes observed that when the intracranial pressure was suddenly raised the animals lost consciousness and tonic muscular spams developed. Cushing described them as similar to the Kussmaul-Tenner type. It is probable that the tonic spasms seen by Cushing and others, representing as they may the decorticate reactions following general cortical ischemia, are identical with the tonic spasms termed the "cerebellar fit," and that the mechanism in each is identical.

The extreme susceptibility of the cortex to anoxia, long acknowledged, has recently been measured with accuracy. It is known that cessation of the heart beat in the Adams-Stokes syndrome, for instance, causes loss of consciousness in ten to fifteen seconds and that convulsions follow if the asystole is prolonged to from twenty to forty seconds.[48] Sugar and Gerard[49] and Simpson and Derbyshire[50] found that the spontaneous action potentials of the cortex disappeared in less than twenty seconds after occlusion of the four major arteries of the head. Weinberger, Gibbon and Gibbon[51] observed that clamping the pulmonary artery in cats produced muscular spasms within ten to twenty seconds after occlusion of the artery. Furthermore, Gerard[52]

48. Formijne, P.: Apnea or Convulsions Following Standstill of the Heart, Am. Heart J. **15**:129, 1938.

49. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938.

50. Simpson, H. N., and Derbyshire, H. J.: Electrical Activity of the Motor Cortex During Cerebral Anemia, Am. J. Physiol. **109**:99, 1934.

51. Weinberger, L. M.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation to the Central Nervous System: Physiologic Effects, Arch. Neurol. & Psychiat. **43**:615 (April) 1940.

52. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938; Brain Metabolism and Circulation, A. Research Nerv. & Ment. Dis., Proc. **18**:316, 1938.

and Dixon and Meyer [53] established that the respiratory rate of the cerebral cortex exceeds any other portion of the brain. The cortex is, therefore, the most susceptible portion of the brain to lack of oxygen and is affected by degrees of ischemia tolerated by other portions of the brain.

Armed with the experimental information that increased intracranial pressure causes cortical ischemia, that cortical ischemia expresses itself in the form of convulsions under certain conditions and that, as pointed out, decortication in man yields motor patterns almost indistinguishable from those seen in lower animals after decerebration, it becomes possible to explain the wide variety of convulsive phenomena seen in patients with cerebellar tumors. It would seem that in the different types of convulsions there is evidence of cortical hyperactivity as well as of cortical release. As will be shown, there is sound experimental evidence that anoxia may affect the cortex in various ways, depending on the participation of a number of variables.

The precipitating increase in intracranial pressure may be brought about by movement, coughing, sneezing, straining at stool, expelling an enema or any other activity that increases the intracranial venous pressure and therefore the general intracranial pressure. The chain of events that follow is dependent on the intensity and rapidity of the rise in intracranial pressure so produced, the height of the existing intracranial pressure, the rapidity with which the vasomotor compensations take place, the extent to which compensatory rises in systemic blood pressure have already occurred, the presence or absence of disease of the cerebral vessels, the age of the patient and the secondary effects of the convulsions themselves on the cerebral blood flow and oxygen saturation of the arterial blood. There are probably many other factors, not as obvious, that also alter the reactions.

With only slight or moderate rises in the intracranial pressure as a consequence of one of the precipitating factors, the circulation through the cortical vessels is for a time slowed, with an increase in the difference in the oxygen contents of arterial and venous blood. Wolff [54] has pointed out that the cortical vessels show the first effects of pressure ischemia, while the deep vessels still contain an adequate circulation. In this interval, before the compensatory mechanisms come into play, the cortical ischemia may occasion different phenomena, depending on the variables mentioned. It is known that neural anoxia first causes heightening of physiologic activity. This early, but transient, exaltation of func-

53. Dixon, T. F., and Meyer, A.: Respiration of the Brain, Biochem. J. **30**: 1577, 1936.

54. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936.

tion may amount in a peripheral nerve, as Heinbecker [55] has shown, to an increase of 50 per cent. The period of hyperirritability is followed by functional depression. Sugar and Gerard observed a marked increase in the magnitude and rate of the spontaneous cortical potentials for a few seconds after clamping the four major arteries to the head. Bronk [56] and Bronk and Thorner [57] also observed the great exaltation in nerve function as an early response to anoxia. This peculiarity of nerve tissue, no doubt, provides the explanation for the so-called asphyxial convulsions which occur in the early stages of asphyxia from whatever cause. Since cerebral ischemia means cerebral anoxia, the generalized clonic convulsions that occur in patients with cerebellar tumor are fundamentally of an asphyxial character and represent the stage of cortical hyperexcitability. In a few minutes or less, however, the compensatory mechanisms respond to the cerebral ischemia. The systemic blood pressure rises; capillary blood flow becomes adequate, and the fit is terminated. The convulsions themselves tend to decrease the oxygen saturation of arterial blood by causing respiratory embarrassment, and thus the effect is exaggerated. Himwich, Bowman, Fazekas and their associates [58] have recently demonstrated that during the convulsion induced by metrazol the oxygen saturation of arterial blood falls as low as 40 per cent. It is this anoxemic burden superimposed on an organism attempting to mobilize its reserves in overcoming cerebral ischemia that probably explains why death so frequently follows convulsions in patients with cerebellar tumor. The cyanosis of these patients during the convulsions is evidence of the convulsive anoxemia.

On the other hand, the response may be loss of consciousness, or syncope. Whether this represents a different response to the same insult, due to one of the variables mentioned, or whether it represents more or less severe cortical anoxia is difficult to determine. On the face of it, loss of consciousness suggests the obtunding of function. This apparent discrepancy has its counterpart in other asphyxial states in which fainting may represent the first response. It is also well known that in insulin shock therapy, in which cortical oxidation is depressed

55. Heinbecker, P.: Effect of Anoxemia, Carbon Dioxide and Lactic Acid in Electrical Phenomena of Myelinated Fibers of the Peripheral Nervous System, Am. J. Physiol. **89**:58, 1929.

56. Bronk, D. W.: The Influence of the Circulation on the Activity of the Nerve Cells, A. Research Nerv. & Ment. Dis., Proc. **18**:298, 1938.

57. Bronk, O., and Thorner, M.: Unpublished data; cited by Bronk.[56]

58. Himwich, H. E.; Bowman, K.; Wortis, J., and Fazekas, J.: Metabolism of the Brain During Insulin and Metrazol Treatment of Schizophrenia, J. A. M. A. **112**:1572 (April 22) 1939. Himwich, H. E.; Bowman, K.; Fazekas, J., and Orenstein, L. L.: Effect of Metrazol Convulsions on the Brain Metabolism, Proc. Soc. Exper. Biol. & Med. **37**:359, 1937.

due to the withdrawal of the substrate dextrose, the initial neural response may be evidenced in loss of consciousness or coma or in violent convulsions. This feature was also noted by Fraser and Reitmann [59] and by Himwich, Alexander and Lipetz [60] in the experimental treatment of schizophrenic patients with very low oxygen mixtures. It seems reasonable to suppose that when syncope is due to cerebral ischemia secondary to an increase in intracranial pressure it represents a more benign phenomenon, since the secondary anoxemia due to respiratory embarrassment is lacking.

The convulsions affecting only one side of the body or the upper or the lower extremities alone are more difficult to explain. However, it is well known that a process acting diffusely or generally on the brain may result in focal or restricted convulsions. Unilateral convulsions have been seen in cases of asphyxiation [61] produced by an anesthetic, as well as in insulin convulsions. The underlying cause for the unusual vulnerability of one hemisphere, or even an isolated portion of the motor cortex, is not clear in any of these instances. One can only speculate concerning the possibility of variations in the arterial distribution, of abnormalities in the circle of Willis, of localized disease of the cerebral arteries, of previous disease rendering a certain area of the brain more susceptible to injury or, finally, of some constitutional difference between the hemispheres. Whatever may be the ultimate explanation for the lowered epileptogenic threshold of one hemisphere or of some portion of the motor cortex, such as the facial area, it is nevertheless, a clinical fact that unilateral or intensely focal convulsions may occur in the presence of a process acting diffusely. The appearance of unilateral convulsions, therefore, need not eliminate the possibility that a cerebellar tumor is present. Experience has shown that cortical disturbances cause clonic convulsions, but it has apparently been insufficiently recognized that cortical ischemia produced by intracranial pressure may be an excitant as well as a depressant of the cortex.

In view of the foregoing observations the mechanism of the tonic fit suggests itself. If the increase in intracranial pressure is already high and of some duration, the cortex may be rendered ischemic by a sudden rise in the intracranial pressure provoked by straining at stool or attempting to expel an enema. This situation is comparable to the

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59. Fraser, R., and Reitmann, F.: A Clinical Study of the Effects of Short Periods of Severe Anoxia with Special Reference to the Mechanism of Action of Cardeozol, J. Neurol. & Psychiat. **2**:125, 1939.

60. Himwich, H. E.; Alexander, F. A. D., and Lipetz, B.: Effect of Acute Anoxia Produced by Breathing Nitrogen on the Course of Schizophrenia, Proc. Soc. Exper. Biol. & Med. **39**:367, 1938.

61. Walker, F.: Convulsion Commencing in the Face and Hand from the Influence of Nitrous Oxide Gas, Lancet **1**:984, 1882.

sudden, complete blanching of the cortex produced experimentally by Cushing and by Forbes and Wolff with abrupt increases in intracranial pressure. The resulting profound cortical ischemia, for a period, produces physiologic decortication and is evidenced in man, as in animals, by the tonic convulsion. As indicated earlier, the motor patterns following decortication in man may be indistinguishable from those following decerebration in animals. It is this confusion that seems to have given rise to the suspicion that the "cerebellar fit" actually represents a decerebration phenomenon. The release of the lower tonic postural centers from cortical control indicates the severity of the cortical ischemia. The respiratory embarrassment plus the possibility of temporary asystole of the heart due to vagal stimulation produces a further fall in the oxygen saturation of the arterial blood. If the compensatory mechanisms are too depressed death occurs. The frequency of death following the cerebellar fit has been commented on by Bailey [2] and by Grinker.[13] Conversely, if the medullary centers are not too depressed the blood pressure rises again; the heart is released from effects of vagal stimulation, as observed by Cushing in experimental animals, and the subject recovers as the cerebrum is adequately oxygenated. The jamming of the medulla into the foramen magnum by the sudden increase of pressure may further add to the anoxic insult, because local compression of the vasomotor and respiratory mechanisms in the medulla impairs their capacity to react to cerebral ischemia. Moreover, the anoxemia resulting from the respiratory spasm depresses already depressed centers. The lowered oxygen tension of the arterial blood starts a vicious circle, ending in respiratory failure. A common observation is that respiration usually ceases before the heart beat.

From this point of view, the "cerebellar fit" is seen to be an extreme form of physiologic decortication, the lesser manifestations of which are expressed as syncopal episodes or as clonic convulsions.

SUMMARY

While fits have been thought to be of unusual occurrence in association with cerebellar tumors, study of 158 cases of verified tumors of the cerebellum disclosed their presence to be not infrequent.

Although the tonic fit is supposed to represent the usual pattern of convulsions occurring in association with cerebellar tumors, study of the literature as well as of our own cases disclosed that every possible variety of fit may occur.

The various theories which have been offered to explain the so-called cerebellar fit are discussed. It is pointed out that although the convulsions are popularly supposed to represent decerebration, there is no evidence that this occurs. In fact, all the phenomena noted in the

so-called decerebrate fit can be produced by decortication alone. Decortication may be produced through the medium of temporary cortical ischemia resulting from transitory alterations in the intracranial pressure.

The physiologic evidence supporting this contention is reviewed. Since cerebral ischemia may act as a temporary cortical excitant as well as a depressant, the clonic convulsions noted in a number of cases are accounted for. The changes in cerebral blood flow secondary to alternations in the intracranial pressure may account for all varieties of convulsive phenomena observed.

All types of fits may occur in patients having a tumor of the cerebellum, and the presence of focal or generalized convulsions does not exclude the diagnostic possibility of such a lesion.

Case Reports

THE VISUOPSYCHIC APPARATUS AND THE ACCOMMODATION REFLEX

R. Yorke Herren, M.D., Ph.D., Portland, Ore.

Recently a case was observed which illustrates an infrequently encountered physiologic phenomenon.

REPORT OF CASE

R. F., a foreign-born Italian aged 55, who was strongly right handed, was admitted to the hospital with the history that for a year and a half he had complained of ever increasing headache. During the course of his illness there had developed personality changes in the direction of delusions, loss of orientation in all three spheres, extreme personal untidiness and loss of judgment. Several years before admission he had suffered a burn of his left cornea, the resulting scar leaving him blind in that eye.

Examination.—On admission the patient was disoriented, highly uncooperative and extremely dehydrated, with an irregularly reactive right pupil. The pupil and internal structures of the left eye were completely obscured by a milky white corneal opacity. The right optic disk showed choking of 4 D. The visual fields could not be determined, since the patient spoke no English and was extremely uncooperative. The left eye showed internal strabismus. Otherwise the cranial nerves were intact. The patient exhibited generalized weakness, more marked in the left leg, which was edematous. There was marked muscular tenderness in the calf and thigh of the left leg; otherwise sensation appeared to be the same on the two sides. Cerebellar tests revealed no evidence of system involvement. The tendon reflexes of the upper extremities were present, normal and equal on the two sides. The knee and ankle jerks were hypoactive on the left, and there were a few clonic jerks of the right ankle.

Because of the edema of the left leg a primary neoplasm was suspected; thorough search, however, did not reveal anything, and the edema and tenderness of the left leg subsided.

Stereoscopic roentgenograms of the skull showed that the pineal gland was displaced downward and backward.

Operation.—The patient's condition became grave. Ventriculograms revealed a cyst in the left occipital region containing xanthochromic fluid and debris. Immediately after this examination craniotomy was performed. Block dissection of the tumor and adjacent portion of the brain was made. One arm of the incision parallelel the falx, for about 2 cm. down on the convexity; another arm was at right angles to the first at about the junction of the parietal and the occipital lobe. These incisions were extended until they met in the cavity of the left ventricle. A third incision, at right angles to the plane of the preceding two and parallel to the tentorium, encompassed the major part of the tumor. Thus, the calcarine cortex was left intact, but practically all of Brodmann's areas 18 and 19 on the convexity of the left hemisphere was excised.

Course.—Considering his general debility, the patient made a good postoperative recovery. As soon a he began to talk, it was learned through an interpreter

that he stated he was blind. Light responses were present in his seeing, or right, eye. He made no attempt to dodge a finger when it threatened his eye. He did not recognize any of his family or friends unless he was given extravisual sensory cues, such as the sound of a voice or of his daughter's step. His daughter was particularly faithful to him and fed him most of his meals. In the middle of a meal, when a spoonful of food and a flower were offered simultaneously, he was as likely to accept the flower in his mouth as the food. A few bites of some such substance allowed him to recognize its unpalatability, and he would spit it out and berate his daughter. However, when the spoon was again presented, he might reach for the curtain pole about his bed, an object at least 10 feet (304 cm.) away; or if his head had been turned in expelling the unpalatable material and his daughter coaxed him to take the food in his hand, he might reach for utensils on the bedside stand or a second relative standing nearby. His sense of touch immediately informed him of his mistake, and he would then grasp at everything until he recognized the feel of the spoon. His eyes would follow moving objects, and his daughter's clothes, which were usually of vivid colors, always attracted him. However, he would not follow any object for long as it retreated from him. Apparently, he had no mechanism for differentiating his visual clues. In this state it was impossible to get him to focus on any object, since apparently nothing had any visual meaning to him. However, the size of his pupil was observed to change as his gaze roved around when the intensity of light in the room was constant.

He was discharged to enter another hospital, where he was kept a bed patient and died some time later, of pneumonia. Permission for autopsy was refused.

COMMENT AND CONCLUSIONS

This case is one of a strongly right-handed man who for several years had had peripheral blindness in the left eye. A tumor developed in the left occipital portion of the brain in the course of treatment, for which the major portion of Brodmann's areas 18 and 19 of the left hemisphere was removed, leaving area 17 intact. Postoperatively mind blindness developed, but he retained his ability to receive visual sensory impressions. The mechanism for light reaction and probably that for accommodation were intact. (Attention should be called to the absence of the convergence reflex, which normally would have affected the size of the right pupil had the patient not been blind in the left eye.)

Since the anatomic studies of Campbell [1] and Brodmann [2] clinical cases have been supplied to illustrate that in the neural organization of any single function several portions of the cortex are involved. First an arrival platform or cortex makes possible awareness of sensation. In the visual sphere, bilateral or partial destruction of the occipital cortex, as is well illustrated in the war material reported on by Holmes and his associates,[3] makes for complete blindness or field defects. The

1. Campbell, A. W.: Histological Studies on the Localization of Cerebral Functions, London, Cambridge University Press, 1905.

2. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, Johann Ambrosius Barth, 1909.

3. Holmes, G.: Disturbances of Vision by Cerebral Lesions, Brit. J. Ophth. **2**:353, 1918. Holmes, G., and Lister, W. T.: Disturbances of Vision from Cerebral Lesions with Special Reference to the Cortical Representation of the

(Footnote continued on next page)

second level, as is seen in the often cited experiments of Munk,[4] has to do with the organization of simple sensation and its integration into visual memory or the recognition of the purposiveness of the stimulus. Here, again, each hemisphere appears to be equally represented. The third, and anatomically less well delimited, area has to do with the projection of simple visual memory into future uses and its integration with similarly organized material from the other sensory spheres. It is well recognized that lesions at the third level of integration in the left hemisphere of right-handed persons, in those areas which are the projection centers for the functions of speaking, reading and writing, produce aphasia, alexia or agraphia even though there are an identical anatomic counterpart and adequate anatomic connections in the opposite hemisphere. Similarly, in the visual sphere there is unilaterality of physiologic dominance or vulnerability, as the case may be. As this case demonstrates, the explanation probably lies in the physiologic integration at the third level, despite bilaterality of anatomic integration.[5] These ideas have been developed in the many papers of Head and Henschen for the aphasias, agraphias and alexias and by Orton[6] for the visual sphere.

Thorough perusal of textbooks and the periodical literature fails to reveal any exact residence for the mechanism of the accommodation reflex. Furthermore, no author with any certainty locates the integers of the reflex. The majority of authorities appear to favor the geniculocalcarine bundle as both the corticipetal and the corticifugal pathway. If one accepts the accommodation reflex as intact in this case, perhaps some light is shed on the mechanism. The geniculocalcarine bundle arises in the lateral geniculate body and swings laterally and upward to pass in the retrolenticular portion of the internal capsule. It then passes medially and backward under the posterior body of the lateral ventricle. This course is continued backward medial to the median ventricular wall until the bundle ends in the lips of the calcarine sulcus. The efferent fibers in this bundle probably have the same course, but terminate not in the lateral geniculate body but in the midbrain, in the group of nuclei of the third nerve. The median ventricular wall was spared in this operative procedure, as the ventricle was entered but not crossed. Since area 17 was practically the only visual cortex remaining, this structure and these pathways are offered as the probable mechanism for the accommodation reflex. There does not seem to be any reason for supposing that an intact dominant hemisphere is necessary for this fundamental reflex.

Dr. W. P. Van Wagenen, Rochester, N. Y., made available the material for this report.

Macula, Brain **39**:34, 1916. Holmes, G., and Horrax, G.: Disturbance of Spatial Orientation and Visual Attention with Loss of Stereoscopic Vision, Arch. Neurol. & Psychiat. **1**:385 (April) 1919.

4. Munk, H.: Die Functionen der Grosshirnrinde, Berlin, A. Hirschwald, 1881.

5. Tilney, F., and Riley, A. H.: The Form and Function of the Central Nervous System, ed. 3, New York, Paul B. Hoeber, Inc., 1938.

6. Orton, S. T.: "Word-Blindness" in School Children, Arch. Neurol. & Psychiat. **14**:581 (Nov.) 1925.

APPARENT DEDIFFERENTIATION OF NERVE CELLS OF THE HUMAN BRAIN AS A RESULT OF PROLONGED STARVATION

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Investigations of the effects of starvation on the human nervous system are not numerous, and few reports have appeared in recent years. It has seemed worth while, therefore, to record the changes observed in the nerve cells of the brain of a man who refused food over a long period and who died in a state of extreme emaciation.

Jackson [1] summarized the observations of the earlier workers in his comprehensive volume on inanition. Popow [2] reported hemorrhagic extravasation, proliferation of neuroglia and atrophy and cloudy swelling of the ganglion cells in the brain of a man dying of starvation as a result of esophageal stricture. Tarassewitsch [3] described cytoplasmic vacuolation and pigmentation in the cells of the cerebral cortex and slight chromatolysis in the Purkinje cells of the cerebellum after thirty-five days of inanition in the case of a religious fanatic. He did not see any complete breaking down of the cells.

Meyer [4] reported on the brain of a man who refused food for sixty days. The brain was edematous and weighed 1,600 Gm. Meyer observed that some of the cells were mere remnants and that all were surrounded by wide, clear zones. He did not see any phagocytic activity. Hassin [5] described the brain of a man who died in the Russian famine. He observed that a few ganglion cells in the cerebral cortex were somewhat swollen, but that the Nissl bodies, as examined in the cells of the motor region, the pons and the cerebellum, were well preserved. The nuclei of the cells were rather pale and sometimes dislocated, and the nuclear membrane was folded. He said of the caudate nucleus (page 553):

> The ganglion cells were markedly swollen, the chromatin substance was broken up, especially in the center, and often was in a state of dissolution, the cell body appearing discolored and vacuolated. . . . Many of the changed cells had been invaded or surrounded by glial cells.

From the Department of Anatomy, Baylor University College of Medicine.

1. Jackson, C. M.: The Effect of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Co., 1925, chap. 10.

2. Popow, L.: Addition to Dr. Ruppert's Article, "Case of Stricture of the Esophagus" and Examples: A Few Notes on the Process of Hunger in General, in Investigations and Notes of the Therapeutic Clinic Hospital, Warsaw Imperial University, 1885, p. 65; cited by Jackson.[1]

3. Tarassewitsch, L. A.: Russ. Arch. f. Path. **5**:687, 1898; cited by Jackson.[1]

4. Meyer, A. W.: J. M. Research **36**:51, 1917.

5. Hassin, G. B.: Brain Changes in Starvation, Arch. Neurol. & Psychiat. **11**:551 (May) 1924.

REPORT OF A CASE

History.—A white man aged 46 was admitted to the Lenwood Veterans' Hospital, in Augusta, Ga., on July 14, 1938. He apparently was suffering from a manic-depressive psychosis. For more than seven and a half months he had refused to take food and had frequently to be fed by force. Even when thus fed he often regurgitated the food. When intravenous injection of dextrose was attempted, he removed the needle if possible. Under these conditions he wasted to an extreme degree and died early in March 1939.

Pathologic Observations.—The anatomic diagnosis was: severe emaciation; carbuncle in the right mastoid region; multiple furunculosis of the trunk, and chronic adhesive pleuritis.

The body was markedly undernourished and emaciated. There had been such marked absorption of the orbital fat that the eyeballs were sunk deep in their sockets. The subcutaneous tissue showed practically no fat. On both sides of the thorax there were many thick, fibrous adhesions of the parietal and the visceral pleura. The pleural cavity was free of fluid. The lungs were normal. The right lung weighed 370 Gm., the left 350 Gm. The heart was small, weighing 200 Gm. It was normal except for thickening of the chordae tendineae. The liver weighed 910 Gm. and showed no pathologic changes. The stomach was removed, but careful investigation revealed no lesions. The kidneys were grossly normal; each weighed 130 Gm. The spleen weighed 100 Gm. and was grossly normal. The brain weighed 1,240 Gm. There were no gross pathologic changes, either of the brain or of the meninges.

Microscopic Observations.—Specimens of brain tissue from the motor region of the frontal cortex, from the occipital cortex and from the cortex of the lateral cerebellar hemispheres were fixed in dilute solution of formaldehyde U.S.P. (1:10), dehydrated in alcohol, cleared in xylene, embedded in paraffin and sectioned at 10 microns. The sections were stained for seventy-five minutes in a 1.5 per cent aqueous solution of cresyl violet.

Observations on the cerebral cortex with low power magnification revealed little except marked paucity of nerve cells in the deepest layer, the layer of polymorphic cells, and proliferation of glia. It was also noted that the nuclei and the cytoplasm of the pyramidal cells were not well differentiated.

Observation with an oil immersion lens showed striking changes in both the cytoplasm and the nuclei of the cells of all layers. The cytoplasm of many of the cells was hypochromatic and vacuolated. That of others appeared to be undergoing a process of dissolution, beginning in the center of the cell, around the nucleus. In many cases, especially in the layer of polymorphic cells, this process had proceeded so far that the nuclei of the nerve cells seemed as naked as those of the glia cells. Many instances of neuronophagia, of invasion or encroachment of the glia cells on the ganglion cells, were observed.

The most interesting cytologic changes, however, occurred in the nuclei of the nerve cells. In the majority of the nerve cells the nucleolus, instead of occupying the usual central position, was far out on the border of the nucleus, in contact with the nuclear membrane (fig. 1). This is a condition which occurs in some of the cells of "normal" persons. The eccentric position, with the nucleolus on the nuclear membrane, was not found, however, in more than 10 of 100 cells in counts which I made on persons dying of various causes. In the present case, it was noted in 70 of 100 cells, even in cells the cytoplasm of which was well preserved. It was the position of the nucleolus in practically all the cells in which the cytoplasm had undergone dissolution or had been phagocytosed.

A change which altered still further the appearance of the nuclei was the accumulation of deeply basophilic granules. Normally the nucleus of the nerve cell contains few or no such granules. It may be almost completely clear, or it may de diffusely basophilic, depending probably on its physiologic state.[5a]

Accumulation of the basophilic granules occurred concomitantly with dissolution of the cytoplasm. The result of these two processes, together with the eccentric position of the nucleolus, gave the "final stage" to which I could trace the nucleus of the nerve cell, a stage common in the layer of polymorphic cells, a great resemblance to the nuclei of the glia cells. In fact, under a low power lens it was impossible to distinguish the naked, metamorphosed nuclei of nerve cells from the glia cells surrounding them.

Whether or not the nucleolus of the nerve cell was eventually extruded or lost in some other way I cannot say with certainty at present. There were

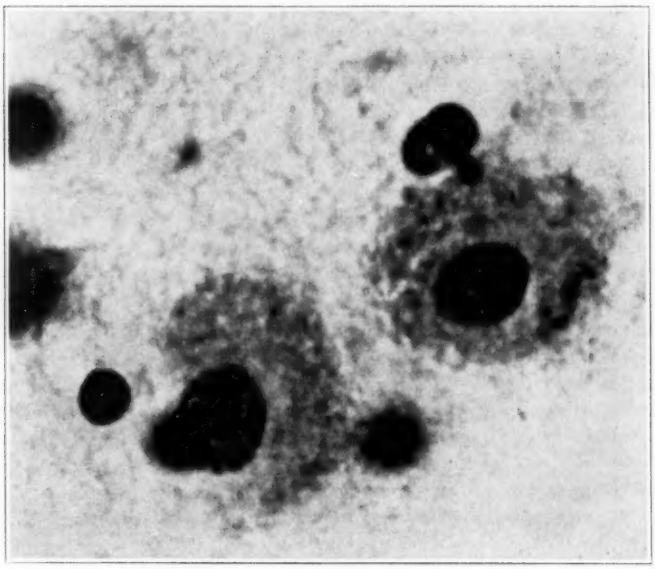

Fig. 1.—Two cells from the layer of polymorphic cells of the cerebral cortex of the brain described here. The cytoplasmic dissolution has begun. The cells are swollen, prior to dissolution of the cytoplasm. In the cell on the left the eccentric nucleolus is seen. In the cell on the right accumulation of basophilic granules is well advanced.

numerous nuclei which closely resembled the altered nuclei of nerve cells in which no nucleolus could be found, and many of these, even with an oil immersion lens, could not be definitely identified as to their neuronal or glial nature.

In the Purkinje cells of the cerebellum the changes were not as striking, but were still marked. None of these cells showed discrete granules of Nissl material. They were either small, hyperchromatic cells with shrunken outlines or large, swollen, edematous, hypochromatic cells, such as Dolley[6] and I[7] have

5a. Andrew, W.: Am. J. Anat. **64**:351, 1939.

6. Dolley, D. H.: J. M. Research **24**:309, 1911.

7. Andrew, W.: Ztschr. f. Zellforsch. u. mikr. Anat. **27**:534, 1937.

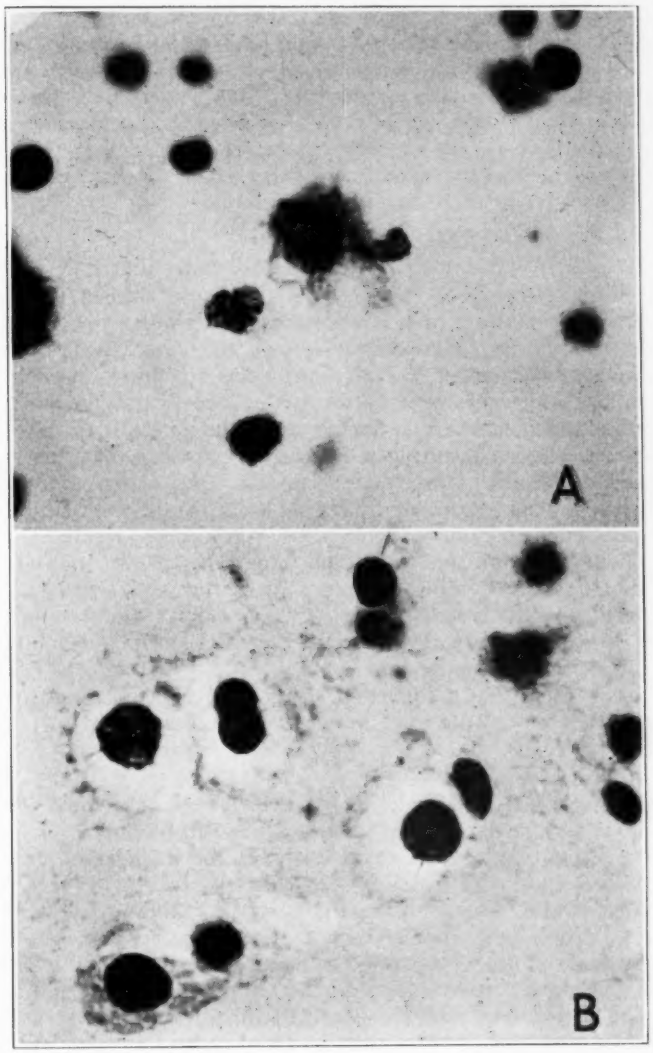

Fig. 2.—*A*, a pyramidal cell from the cerebral cortex. The nucleolus is eccentrically placed at the outer edge of the nucleus, and there are many basophilic granules in the nucleus. The cytoplasm is vacuolated and degenerating.

B, nuclei of three polymorphic nerve cells in an advanced stage of the metamorphosis described here. The nerve cell in the lower left corner still has considerable cytoplasm about it, but the other two (the one in the upper left corner, the other just below and to the right of the center) are practically naked nuclei. No nucleoli are seen, and the nuclei resemble those of large glia cells. The smaller nuclei in the field are those of true glia cells.

described as late stages in the fatigue of nerve cells. Among the hypochromatic cells were many instances of vacuolation of the cytoplasm similar to that seen in the cerebral cortex, but not of such an advanced degree.

The most conspicuous change in the nuclei of the Purkinje cells was the accumulation of basophilic granules, which were abundant in the majority of them. The eccentric position of the nucleolus was common, but not so much so as among the cells in the cerebral cortex. The nuclei of the granular layer were in closer relation than normal to the Purkinje cells, as though the Purkinje cells had sunk back toward the deeper layer or the nuclei of this layer had moved outward. Thus, in some instances a number of the nuclei of the granular layer were actually superficial to the Purkinje cells.

COMMENT

The changes in the nerve cells in the present case, in which the patient died of inanition, are in some respects similar to, and in others wholly different from, changes previously described by other authors.

Rosenbach [8] observed vacuolation and shrinkage similar to the cytoplasmic changes in my material. As in my case, the polymorphic cells seemed more strongly affected than the pyramidal cells. Coen,[9] studying the changes resulting from inanition in 3 rabbits and a kitten, observed cytoplasmic atrophy, but no nuclear changes. Donaggio [10] noted frequent vacuolation of the nerve cells in adult rabbits subjected to the combined factors of cold and starvation. Asada [11] reported marked congestion of the brain and other organs in starved rabbits, but did not describe cytologic changes in the brain.

In previous experimental work on mice with acute inanition,[12] I observed loss of Nissl material, shrinkage of the cells, basophilia of the nuclei and active neuronophagia.

One sees, then, that cytoplasmic changes in nerve cells during inanition have been reported in a number of instances, although the degree and kind of change described show some variation from one author to another.

It is, however, in the nuclei of the neurons that the most interesting change occurs. The cytoplasmic changes seem to be only of a degenerative nature, their final result being to leave the nucleus in a naked, or almost naked, state, the condition in which it was in its early history. The return of the deeply basophilic property and, above all, of the numerous basophilic granules, together with the loss or obscuring of the nucleolus, makes this naked nucleus indistinguishable from the nuclei of the more primitive cells of the nervous system.

The alteration reported in the literature which corresponds most closely with that seen here is perhaps Nissl's profound cell change, in which there are distinct degeneration of the cytoplasm and hyperchromatosis and decrease in size of the nucleus (Penfield [13]). In Nissl's

8. Rosenbach, P. I.: Centralbl. f. Nervenh. u. Psychiat. **7**:33, 1884.
9. Coen, E.: Bull. d. sc. med., Bologna **7**:666, 1890.
10. Donaggio, A.: Arch. ital. de biol. **46**:437, 1907.
11. Asada, H.: Am. J. Physiol. **50**:1, 1919.
12. Andrew, W.: J. Comp. Neurol. **70**:413, 1939.
13. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932.

cell change, however, the nuclear changes do not lead to the glia-like end stage seen in my material.

Changes somewhat similar to those seen in this case have been observed in other conditions (Wertham and Wertham,[14] plate 6, page 545), but none have been so radical as to leave the nuclei of the nerve cells actually indistinguishable from those of the glia cells.

The more considerable changes seen in this case may be explained by the fact that here one is dealing with a case of prolonged partial starvation, whereas most of the earlier study has been in cases of acute inanition.

Consideration of this process leads one to a number of interesting speculations. How long do the metamorphosed, naked nuclei of the neurons survive and continue their life processes? Judging from the large number present, they may do so for a considerable length of time. If so, how far is one justified in speaking of this process as actual "dedifferentiation," such as that which is undergone by a number of less highly specialized cell types under the proper conditions? Observation of such a process in the nerve cell may force one to revise the concept that this cell is so highly differentiated as to be wholly unable to return to a more primitive condition. The view of Friedman,[15] one of the early investigators, is interesting in this regard. He reported mitoses in nerve cells and assumed that they underwent transition to a more primitive type of cell before showing such mitosis. The only well substantiated report of mitoses in ganglion cells, however, is that of Schreiber and Wengler,[15] who observed stages of early mitosis in nerve cells of the retina of the rabbit after injection of scarlet oil into the anterior chamber of the eye.

While in my material I have seen no evidences of division, the nucleus appears almost identical with those of the more primitive cells of the nervous system, which, as is known, are wholly capable of undergoing mitosis.

This nuclear metamorphosis would seem also to be of interest in relation to the reports on "giant glia cells" or "giant glia nuclei," both in pathologic and in experimental conditions. Bertrand and Gruner[16] observed a peculiar type of glia cell in the brains of rabbits after the injection of benzopyrene. Of the size of the nuclei of these cells, they said (page 637): "The nuclei of the giant glia cells may reach a size ten times that of the nucleus of an astrocyte." They possessed, also, eccentric nucleoli (peculiar cell organs for glia cells of any type, according to present knowledge!); "others contained a delicate network of chromatin granules arranged in rays around a small, eccentric nucleolus." Many points in the description of these giant glia nuclei make it seem possible that the naked nuclei of nerve cells have at times been mistaken for glia nuclei.

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14. Wertham, Frederic, and Wertham, Florence: The Brain as an Organ, New York, The Macmillan Company, 1934.

15. Cited by Wertham and Wertham,[14] p. 333.

16. Bertrand, I., and Gruner, J.: Compt. rend. Soc. de biol. **128**:637, 1938.

SUMMARY

Marked changes, apparently in the direction of dedifferentiation, were observed in the nerve cells of the brain of a man who died of inanition. In the cerebral cortex there was vacuolation of the cytoplasm of the cells with eventual dissolution or phagocytosis, leaving many naked nuclei. A peculiar series of changes occurred in the nuclei of the nerve cells which left them in a condition in which they were practically indistinguishable in Nissl preparations from some of the glia nuclei.

The Purkinje cells in the cerebellum showed no discrete Nissl granules. They presented vacuolation and nuclear changes similar to, but less marked than, those in the cells of the cerebral cortex.

CRANIOPHARYNGIOMA IN THE THIRD VENTRICLE OF THE BRAIN

Partial Surgical Removal and Pathologic Study

HOWARD ZEITLIN, M.D., AND ERIC OLDBERG, M.D., CHICAGO

Calcified "flakelike" shadows seen roentgenologically in the suprasellar region have long been recognized as almost positive evidence of the presence of a craniopharyngioma. The lesion arises from the unobliterated portion of the fetal craniopharyngeal duct and usually appears in the form of a cystic tumor. These tumors have been variously referred to in the literature as adamantinoma, suprasellar cyst and hypophysial duct or Rathke's pouch tumor.

Embryologically, in the development of the hypophysis cell rests or remnants have been found not infrequently to remain along the line of formation and rotation of the gland (Erdheim,[1] Carmichael,[2] Duffy [3] and others). The hypophysis is formed by the union of an upward evagination of the dorsal pharyngeal wall of the primitive oral cavity and a downgrowth from the brain, the infundibulum. Most commonly these cell rests which give rise to cystic tumors have been located in the region between the floor of the brain and the roof of the sella turcica. Occasionally similar cysts have been described arising within the sella turcica (intrasellar cysts) and in the posterior wall of the nasopharynx of adults and even within the sphenoid bone, as pointed out embryologically by Bailey [4] and described pathologically by one of us (H. Z.).[5]

The case reported here possesses unique neurosurgical and anatomic features. Roentgenologically, the presence of calcified "flakelike" shadows in the suprasellar region (fig. 1), together with the clinical evidence of increased intracranial pressure, suggested the diagnosis of a craniopharyngioma. Initial intracranial exploration failed to disclose any particular pathologic change in the suprasellar region. Later ventriculographic studies revealed a tumor of the third ventricle, which was removed without untoward effects. Microscopically, the cystic tumor proved to be a craniopharyngioma.

Read at a meeting of the Chicago Neurological Society, Oct. 19, 1939.

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine.

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4. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

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REPORT OF A CASE

History.—G. V., a white man aged 21, was referred from the Illinois Eye and Ear Infirmary and entered the Research and Educational Hospitals on Nov. 3, 1937. He complained of headaches, vomiting and visual disturbances. His illness had started two months prior to his admission, when he awoke in the morning with a severe headache located over the frontal portion of the skull. The headaches had recurred at irregular intervals with increasing frequency and lasted from one to ten hours. The severity had remained the same, although of late the pain had frequently moved to the back of the head and neck and was associated at times with projectile vomiting. Before entrance to the hospital the patient had also noticed double vision and buzzing in the ears, which lasted about a week and then disappeared.

Birth and development were normal, and the family history was essentially without significance.

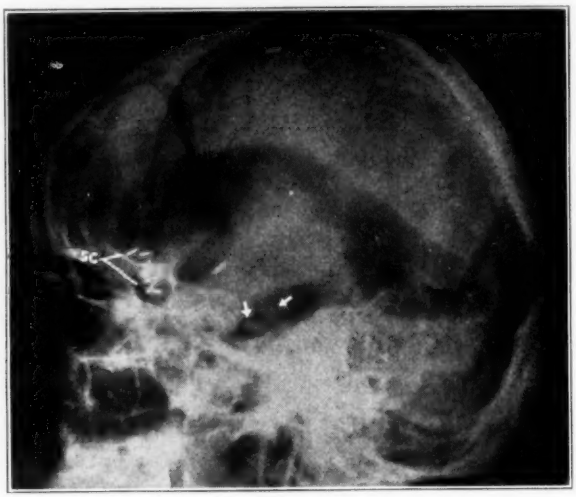

Fig. 1.—Ventriculogram showing dilatation of the lateral ventricle. Arrows indicate areas of suprasellar calcification; *SC*, silver clips seen after the first intracranial exploration.

Neurologic Examination.—The patient was well nourished and responded promptly to questions. He was slightly obese, with a feminine distribution of pubic hair. The face, body and legs were practically devoid of hair. The hands and fingers were long and slender, and the skin was smooth. The feet were high arched. The external genitalia were small.

Percussion elicited moderate tenderness over the posterior surface of the head. Forward flexion of the head and neck met with slight resistance. The patient exhibited some generalized loss of muscle power and hypotonicity. His gait was somewhat unsteady.

The pupils were regular and equal and reacted well to light and in accommodation. The movements of the right external rectus muscle were weak. There were fine, unsustained lateral nystagmus on looking to the left or right and slight rotatory nystagmus to the right on upward gaze. The visual acuity was 0.4 in the right

eye and 0.7 in the left eye. Perimetric studies gave essentially normal results except for slight constriction of the temporal half of the right visual field to the 1 mm. object. The fundi revealed bilateral papilledema, which measured 3 D.

The superficial and deep reflexes were present and equal on the two sides. Pathologic reflexes were elicited in the form of Babinski, Chaddock and Oppenheim signs on the right, with a suggestive pathologic plantar reflex on the left.

Sensory disturbances were essentially absent. The sphincter muscles of the bladder and rectum were intact.

Laboratory Data.—Roentgenograms taken of the skull in the anteroposterior and lateral positions revealed evidence of destruction of the dorsum sellae and indefinite dense shadows in this region, which were suggestive of calcification in a craniopharyngioma.

The Bárány tests gave negative results. The basal metabolic rate was +7 per cent. The Kahn test of the blood gave a negative reaction. The red cell count was 5,200,000; the white cell count, 9,600. Chemical studies of the blood revealed 68 mg. of dextrose and 34 mg. of nonprotein nitrogen per hundred cubic centimeters. The dextrose tolerance test showed a decrease. The preoperative diagnosis was that of a suprasellar cyst bulging into the floor of the third ventricle, chiefly on the right side.

Cranial Exploration.—In accordance with the preoperative diagnosis, a right frontal bone flap was turned down. The brain seemed slightly edematous, although there was no marked increase in intracranial tension. On exposure of the sella the optic chiasm was observed to be markedly prefixed, with the anterior edge virtually abutting the tuberculum sellae. The chiasm seemed much widened, and rather short, stumpy optic nerves, which passed from the chiasm through the optic foramens, were not impinged on in any way. At the posterior boundary of the chiasm the two normal-appearing optic tracts could be seen passing backward. Between the latter the arachnoid membrane was bluish. This was punctured, and ordinary cerebrospinal fluid was obtained. There was no evidence of any cystic condition, and the calcified "flakelike" shadows seen roentgenologically presented a baffling problem. A possible lesion of the chiasm was considered, although the visual fields did not correspond with pathologic changes in the chiasm. It was decided to take new roentgenograms as a possible means of determining more definitely the location of the supposed suprasellar calcification.

Postoperative Course.—The patient made an uneventful recovery, except for edema about the face and eyes, for which there was no definite explanation. The disks showed choking of 1.5 D. on the left and of 1 D. on the right, which later receded completely. The headaches and vomiting disappeared, and the decompression wound was soft and flat. The patient was discharged on Dec. 4, 1937, and was asked to return every two weeks to the clinic. Roentgen therapy was considered, but was not instituted.

Second Admission.—The patient was readmitted to the hospital three months later with similar complaints of headaches and forceful vomiting. He had been working previously as a swimming pool attendant and had made no complaint until the onset of dull headaches in the frontal and occipital regions, which increased in severity. At first they yielded to acetylsalicylic acid, but later they were constant even after medication and rest in bed. While in the hospital the patient had seizures which were characterized by tremor of the body and twitching of the face. He held his mouth open, with a blank expression of the face, and seemed to be confused. When the seizure had passed he did not remember what had happened to him.

Examination: Neurologic signs were essentially normal except for slight blurring of the nasal borders of the disks. The blood pressure was normal.

The possibility of a tumor of the third ventricle was considered at this time, and ventriculographic studies were made. The right ventricle was markedly dilated, and the cerebrospinal fluid was under considerable increased pressure. It was clear and colorless. Seventy cubic centimeters of fluid was removed and 40 cc. of air instilled. Ventriculograms showed marked dilatation of the right ventricle, with no filling of the left and no visualization of the third ventricle. Accordingly, the left ventricle was tapped, and the fluid escaped under increased pressure. About 30 cc. of fluid was removed and 15 cc. of air instilled. Ventriculograms showed little change, as the third ventricle did not fill. Exposures made in the anteroposterior, posteroanterior and lateral positions showed filling of both lateral ventricles. The right ventricle was considerably larger than the left, with encroachment of part of the median aspect of the right ventricle on the left and displacement of the left ventricle to the left side.

The patient left the operating room in good condition, but on the same day there developed left hemiparesis, which involved mainly the arm, with slight weakness of the left side of the face, of central type. At 4 p. m. he became stuporous. The respiratory rate was 4; the pulse rate was 44, and the blood pressure after marked stimulation gave a systolic response of 120 mm. The patient was given 60 cc. of a 50 per cent solution of sucrose intravenously. That evening the right ventricle was tapped with a long spinal needle, and 40 cc. of blood-tinged fluid and 5 cc. of air were removed. The patient immediately began to respond and asked for water. His condition remained fair. Later the same evening he again lapsed into stupor, with a temperature of 100 F. Paralysis of the left arm returned. He continued to improve except for development of mental changes. He used obscene language, spat at the nurses, was talkative, yelled loudly and had defect of memory. After two weeks the hemiplegia rapidly improved, and he became more quiet; an exploration of the third ventricle was again undertaken.

Second Cranial Exploration.—A segment of bone, 3 cm. in width, was removed from the upper region of the old bone flap, toward its hinge. The dura was then opened and a cortical incision made. The lateral ventricle was entered and illuminated with lighted retractors, the exposure being good and the foramen of Monro appearing directly in the middle of the operative field. When the foramen of Monro was illuminated a dark bluish cyst protruding into it from the third ventricle was immediately seen. The cyst was grasped with a pair of forceps, but it ruptured, emptied and collapsed at once. The wall was exceedingly fragile. The foramen of Monro was in turn dilated and the third ventricle entered. Several small pieces of the capsule were removed for histologic study. The cyst, however, seemed very small after being collapsed, and it would have been impossible to remove all of the capsule without mutilating considerably the region of the third ventricle. Therefore a perforation into the other lateral ventricle was made through the septum pellucidum. Hemostasis was completed and the flap closed. The patient left the operating room in good condition.

Subsequent Course.—The following day the patient responded well. When told about his profanity before operation he remarked that he must have been "out of his head." Edema of the eyelid again developed, but slowly receded. He was up in a wheel chair in ten days and was discharged on April 29, 1938, with excellent recovery and good operative results. He was last seen in September 1939. He had no complaints and stated that he was working hard. Visual acuity was 0.6 in the right eye and 0.7 in the left eye. A small defect persisted in the inferior quadrant

of the right temporal field. The optic disks were essentially normal. There was a definite increase of hair about the pubic region, although the feminine distribution remained the same. The patient further volunteered the statement that he had noticed an increase in the size of the testes and penis.

Microscopic Examination.—The tissue taken for biopsy consisted of several pieces of the cyst wall. It was composed of a loose glial stroma, which in places was lined with several layers of cells. The outer layer consisted of a single row of columnar cells arranged in parallel formation, resembling ameloblasts (figs. 2 and 3). Immediately beneath this layer were a few small, spindle-shaped

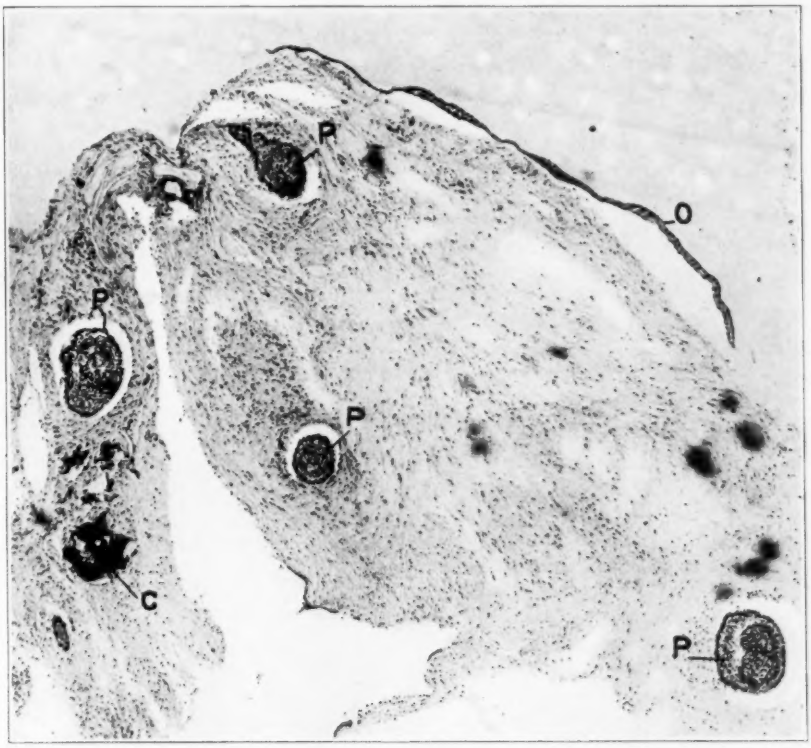

Fig. 2.—Photomicrograph showing the capsule lining of the cyst. *O*, indicates the outer epithelial layer; *P*, papillomatous projections in the cyst wall; *C*, areas of calcification. Hematoxylin-eosin stain; low power magnification.

cells lying at right angles to the columnar cells. The innermost layer of cells was composed of stellate cells with protoplasmic bridges that joined them with neighboring cells. Among the latter cells were nests and pearl formations. These microscopic structures were frequently seen as papillomatous processes embedded in the loose glial stroma (fig. 2). Likewise, there were small, keratinized epithelial pearl formations and deposits of calcium in focal areas. Small capillary blood vessels were scattered throughout the stroma. The microscopic picture was diagnostic of a craniopharyngioma.

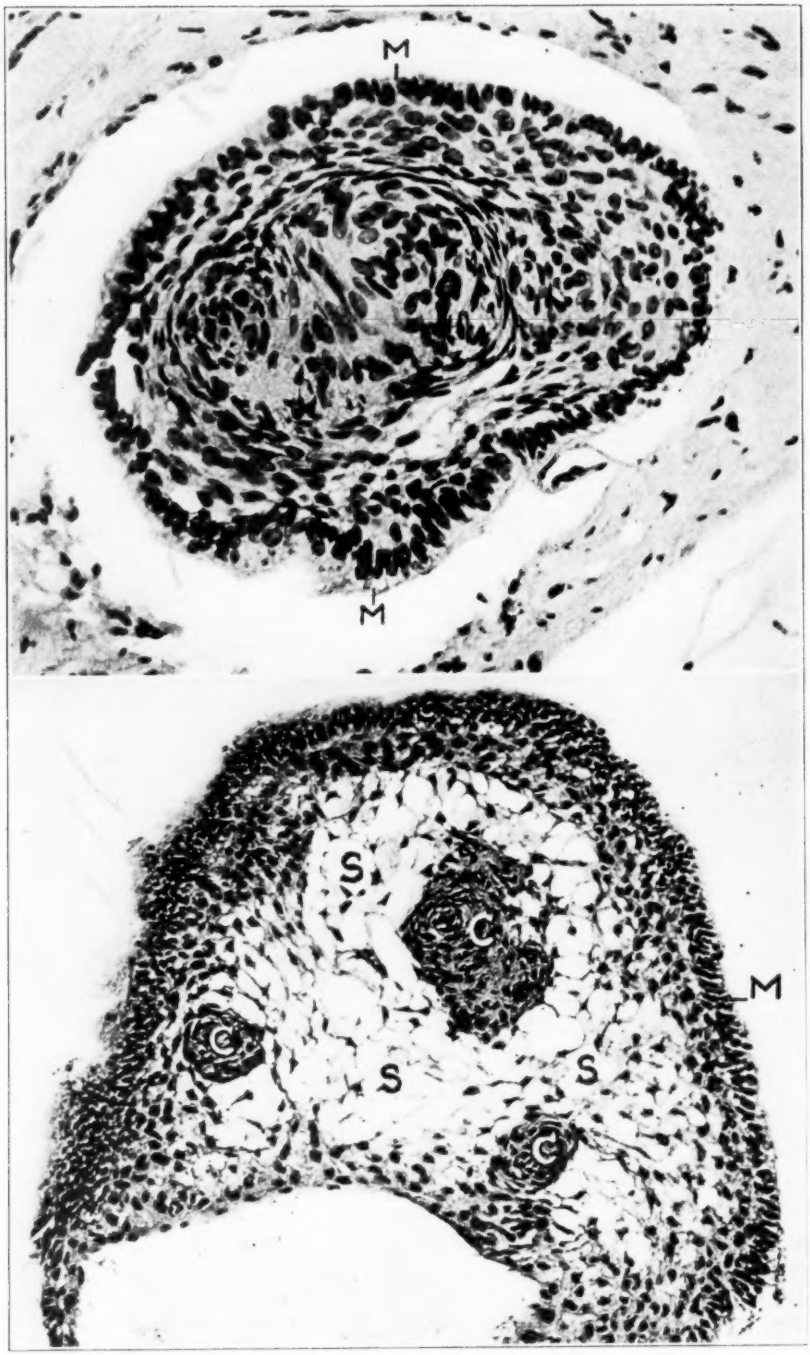

Fig. 3.—Photomicrographs showing the areas *P* of figure 2. *M* indicates the outer layer of parallel columnar cells (ameloblasts); *S*, stellate cells; *C*, concentric whorls. Hematoxylin-eosin stain; high power magnification.

COMMENT AND SUMMARY

The usual presence of calcified "flakelike" shadows in cases of craniopharyngiomas and the rarity of similar shadows in cases of tumors other than the pearly tumors about the sellar region make such shadows almost pathognomonic. However, as has been pointed out by Frazier and Alpers,[6] the identification of the lesion and, as in our case, the determination of the exact location prior to ventriculographic examination and operation are not free from difficulties.

Erdheim [1] demonstrated that in normal persons there are often collections of epithelial cells at the junction of the infundibulum and the base of the brain and at the junction of the infundibulum and the hypophysis. Erdheim asserted that these are remnants of the embryonic craniopharyngeal duct and was first to suggest that the adamantinomas are in reality tumors of the craniopharyngeal duct. It is in this locality that squamous epithelial neoplasms arise, either from the anterior surface of the infundibulum or from beneath the capsule of the anterior lobe. Critchley and Ironsides [7] have thus divided the adamantinomas into two groups, depending on whether they take origin from the upper or from the lower group of cells. If the tumor arises from the upper group of cells it lies above the sella, extending upward and pushing before it the floor of the third ventricle. These tumors are usually large cystic growths extending from the chiasm to the pons and cover a large portion of the base of the brain. By virtue of their position these tumors compress the optic nerves, chiasm and tracts. The tumors arising from the lower group of cells lie within the sella, deepening it in all directions and compressing the pituitary gland. Frequently, at necropsy the tumor has reached such a size that it has spread upward into the third ventricle, obstructing the latter and resulting in secondary hydrocephalus, regardless of its point of origin.

In our case the tumor probably arose from embryonic nests of cells that were situated within the floor of the third ventricle and presented its cystic formation within the third ventricle without any evidence of a similar growth at the base of the brain, where, as has been mentioned, craniopharyngiomas are usually found.

Dandy [8] described eight types of primary encapsulated tumors, 21 cases of which were in his own series. He mentioned the cases of Selke and of Mott and Barratt, which were described as instances of stratified squamous epithelial tumors of the third ventricle. In not a single case were the characteristic microscopic features of a craniopharyngioma revealed. It has generally been assumed that stratified squamous epithelial tumors are found only among tumors of the hypophysial duct and are therefore external to and beneath the brain.

A case somewhat similar to ours has been recently described by Bailey and Bucy.[9] Roentgenographically, suprasellar calcification sug-

6. Frazier, C. H., and Alpers, B. J.: Adamantinoma of the Craniopharyngeal Duct, Arch. Neurol. & Psychiat. **26**:905 (Nov.) 1931.

7. Critchley, M., and Ironsides, R. N.: The Pituitary Adamantinoma, Brain **49**:437, 1926.

8. Dandy, W. E.: Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

9. Bailey, P.; Buchanan, N. D., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

gested a craniopharyngioma. No tumor was seen on frontal osteoplastic operation. Ventriculographic studies showed a tumor of the third ventricle. A second approach to the third ventricle through the frontal lobe revealed the tough wall of a cyst, from which clear fluid containing crystals of cholesterol was obtained. A portion of the cyst wall was removed. The symptoms later returned, and at a third attempt the tumor was dissected from the surrounding structures, when the sella turcica and the circle of Willis were clearly exposed. The child did not recover from this extensive operation and died on the following day. Autopsy revealed a small remnant of the tumor attached to the left optic tract. The hypophysis could not be found at autopsy. From the autopsy and surgical observations it appears that in the aforementioned case a small portion of the cystic tumor was present at the base of the brain, outside the third ventricle. We surmise that in our case, although the patient was well seventeen months after surgical intervention, only time will tell whether remnants of the craniopharyngioma exist outside the third ventricle. The very aspect of the tumor, which was a thin-walled cyst and collapsed immediately on being grasped, together with the absence of cholesterol crystals speaks, in our opinion, for a benign encapsulated craniopharyngioma arising from cell rests in the innermost portion of the ventricular wall in the floor of the third ventricle.

Of the primary, encapsulated, apparently benign and potentially removable tumors of the third ventricle, Dandy [8] mentioned both the solid and the cystic forms. The solid tumors, some of which may be associated with partial cystic formations, arise from the subependyma, the ependyma and the choroid plexus and from embryonic cell rests situated within the lining of the ventricular walls. These neoplasms have been variously described histologically in the literature as tumors of the choroid plexus and as ependymal, pineal, dermoid, epidermoid, glial, endotheliomatous and peritheliomatous tumors.

Of the cystic tumors, other than the occasional parasitic cyst, cysts lined with stratified squamous epithelium, simple cysts of the choroid plexus and those of the cavum Vergae and septum pellucidum, the paraphysial cysts [10] of the third ventricle are most interesting and important. To this group of types of benign, encapsulated cystic tumors of the third ventricle we wish to add that in our present case, a craniopharyngioma.

DISCUSSION

DR. ERIC OLDBERG: I cannot add much to the description of this case as Dr. Zeitlin has presented it. He is more sanguine than I am in calling the tumor benign. All one can say is that it is a craniopharyngioma and that such growths are malignant in that one is unable to remove every cell and thereby prevent recurrence. Time will tell whether this tumor will recur.

The operation was a simple exploration of the third ventricle. A cortical incision was made, and the ventricle was entered via the foramen of Monro. The foramen can be dilated easily. In operations on the third ventricle I think it is also good practice deliberately to make an opening in the septum pellucidum, if one does not already exist. I have had success in making an artificial foramen of Monro for a blocked ventricle by this method.

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10. Zeitlin, H., and Lichtenstein, B. W.: Cystic Tumors of the Third Ventricle Containing Colloid Material, Arch. Neurol. & Psychiat. **38**:268 (Aug.) 1937.

DR. PAUL BUCY: I am inclined to agree with Dr. Zeitlin that this tumor is benign and with Dr. Oldberg that it is malignant. It is benign so far as its microscopic appearance is concerned, but it is certainly malignant from a clinical point of view. Although many have observed patients with similar conditions who have been much benefited by operation and have survived for a number of years, there are few, if any, who have been permanently cured. Recurrence is the rule after a variable period. Dr. Zeitlin has mentioned a patient of mine (Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939, pp. 353-358, case 87) who presented a similar clinical picture and with whom an almost identical surgical experience was had. A dramatic recovery followed the surgical evacuation of the cyst and partial removal of the wall. This persisted for almost a year, when symptoms returned which were temporarily relieved by aspiration of the cyst. At a final operation, made necessary by repeated recurrence of symptoms, complete removal was undertaken and resulted in postoperative death. Operation was performed on a second patient (case 88, pp. 358-361) by the transfrontal approach; the cyst was evacuated through an opening in the lamina terminalis. He, too, made a splendid recovery and to date, over three years after the operation, continues to be well. One cannot say why there should be such a difference in the interval between the operation and the recurrence of symptoms in these 2 cases or how long it will be until the second boy returns with headaches and other difficulties. However, I think one can be sure that there will be recurrence and that eventually the tumor will cause death.

I am concerned by Dr. Zeitlin's reference to this growth as a tumor of the third ventricle. That the tumor lay within the cavity of that ventricle I cannot agree. The craniopharyngioma is of non-neural origin. It arises from embryonic epithelial remnants in the glandular portion of the hypophysis entirely outside the nervous system. How it could come to lie within the nervous system, within the third ventricle, is not comprehensible to me. Rather, it develops beneath the floor of the third ventricle and, as it grows, pushes this floor (the hypothalamus) upward on its dorsal surface. The hypothalamus thus becomes very thin, and gliosis occurs within it. Certainly, the tumor which has pushed upward into the region of the third ventricle often can be approached through the foramen of Monro, but in entering the cystic cavity one must pass through the very thin floor of the third ventricle overlying it. Only in the most unusual cases could one be so fortunate as to remove the tumor completely. Attempts at total extirpation, producing as they do serious injury to the hypothalamus and often to the hypophysis as well (see case 87, previously mentioned), are associated with such a discouraging operative mortality that almost all surgeons are now content with evacuation of the tumor and partial removal of the wall, as I feel sure Dr. Oldberg did in this case.

DR. DAVID SLIGHT: In this man, 21 years of age, definite male characteristics are now developing; he had previously shown "female" characteristics. It is interesting if the tumor interfered with sexual development until the age of 21 and now, after removal, male characteristics are developing. I should like to hear what Dr. Oldberg and Dr. Zeitlin have to say regarding the relation of the operative procedure to the capacity for such development at this late date.

DR. ARTHUR WEIL: One might suggest that the general term "craniopharyngioma" should be replaced by one based on a more definite histologic classification. About thirteen years ago, Critchley and Ironside (*Brain* **49**:437, 1926) collected a group of cases of "adamantinomas" and emphasized the difference in behavior of other suprasellar tumors, such as the "squamous epithelial papillary cyst" or more malignant solid tumors. Perhaps, by a more detailed histologic study of these tumors, one might be able to correlate their structure with their benign or malignant character.

DR. HOWARD ZEITLIN: I wish to mention again that at autopsy these craniopharyngiomas all have a similar gross appearance. The capsule consists of a firm, thickened wall, the cavity being filled with clear fluid which contains crystals

of cholesterol. By extension the tumor invades the third ventricle, pushing before it the floor of the third ventricle. Occasionally the cysts rupture through the floor of the third ventricle, causing obstruction with secondary hydrocephalus.

In contrast, the cystic tumor, as seen in our case, consisted of an exceedingly thin and fragile wall, the cavity being filled with clear fluid; cholesterol crystals were absent. The cystic tumor bulged into the foramens of Monro and was attached to the inner floor of the third ventricle. Absence of evidence of a similar growth outside the third ventricle at the base of the brain denotes, in our opinion, that one is dealing with a primary encapsulated craniopharyngioma arising from embryonic cell rests within the innermost wall of the floor of the third ventricle.

The fact that the optic chiasm was markedly fixed at its anterior end to the tuberculum sellae might account for the abnormal position of the embryonic cell rests in this case.

With reference to Dr. Slight's question: In this case, unfortunately, estimates of androgen and estrogen were not made prior to surgical intervention. Perhaps it would be of interest to make such studies now.

Dr. Eric Oldberg: Did I understand Dr. Bucy to say that this cyst must have been on the base of the brain and have pushed up the floor of the third ventricle before it? The cyst was taken out through the foramen of Monro. In that case I should expect histologic remnants of the floor of the third ventricle to have been seen in the specimen, and Dr. Zeitlin found none.

Technical and Occasional Notes

SEALING SPECIMENS OF THE BRAIN WITH PLIOFILM

A Practical and Inexpensive Way to Exhibit Specimens

L. Wallingford Darrah, M.D., Northampton, Mass.

Pliofilm can be used to cover preserved gross specimens of the brain. The accompanying photographs show that an entire brain or any part of it can be so sealed. Such a method permits many persons to examine the object freely, without hardening the hands or fear of damage to the brain. By keeping the specimen in a cool place it can be used for months. Such a method of enclosing specimens is especially suitable for study or teaching purposes. Samples can be slipped into a pocket or handbag and easily taken anywhere without fear of injuring adjacent material.

My experience has been only with brains which have been in a 10 per cent concentration of solution of formaldehyde U. S. P. for at least four weeks. The spinal cord does not appear well when sealed by this method because of its length and the concealment of cross sections. Specimens of the heart, liver, kidneys and other structures might also be so sealed.

The photographs indicate that the pliofilm method is practical. For a small sum an entire brain, a hemisphere and two or three smaller specimens of the brain can be made ready to use. Figure 2 shows the articles required for the method.

MATERIALS NEEDED

Pliofilm.—A roll, 20 by 60 inches (50.8 by 152.4 cm.), sells for 25 cents and should be obtainable in most stationery stores. It is made by the Goodyear Tire & Rubber Co., Inc., Akron, Ohio, and is distributed by the Dennison Mfg. Co., Framingham, Mass. Laboratories requiring larger amounts may prefer the 40 inch (81.6 cm.) width.

Sealcraft Heating Iron No. 10 (for use with pliofilm).—This iron may be obtained in three styles; one has a longer cord, which makes it the most useful. The iron is manufactured by the Dennison Mfg. Co., and the price is $1. It should be on sale at the same store as pliofilm.

Scotch Cellulose Tape (in ¾ inch [1.9 cm.] utility dispenser).—This costs 15 cents and is manufactured by the Minnesota Mining and Manufacturing Co., St. Paul.

Celluloid Foot Ruler.

Scissors.

Hand Magnifying Glass.

From the Northampton State Hospital.

TECHNIC FOR SEALING WHOLE SPECIMENS OF THE BRAIN IN PLIOFILM

Use a brain which has been in a 10 per cent concentration of solution of formaldehyde U. S. P. for at least four weeks. When the brain no longer drips much, hold a small towel or pad beneath so that the solution of formaldehyde will not wet the edges to be sealed. Place the base of the brain on the pliofilm; it will not matter if there is a little solution of formaldehyde beneath the brain,

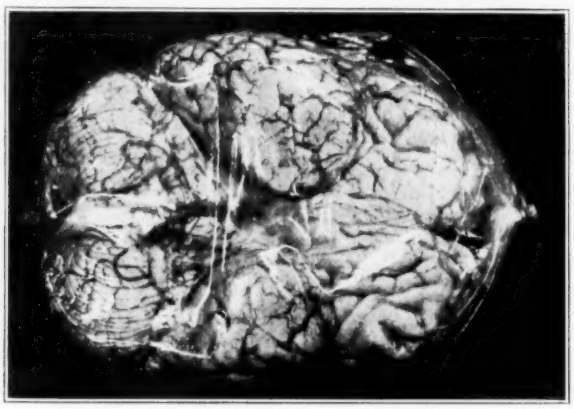

Fig. 1.—Specimen of the whole brain sealed in pliofilm.

Fig. 2.—Photograph showing articles needed for the pliofilm method of sealing specimens of the brain, and various specimens after sealing.

as there should be some moisture with the specimen. As soon as the brain is laid down, pull the pliofilm over the hemispheres to overlap the longitudinal sinus. Do not allow any moisture to form on the edges to be sealed because moisture hinders good sealing and will cause leakage and the specimen will not last. The specimen in figure 1 (also shown far to the left in figure 2) was sealed by placing the celluloid ruler along the superior longitudinal sinus (thus also protecting the specimen from damage by excess heat), lapping the pliofilm tight over it and then sealing. I sealed this specimen without assistance, on a kitchen table under a

bright light. While the upper edge was being sealed, cotton pads close to the brain kept any moisture from seeping to the sides. When the top was firmly sealed with the iron by running it repeatedly along the ruler the cotton was taken from the sides, and the pliofilm was twisted tightly at both ends (see the twisted ends in figure 1 and also far to the left of figure 2); wet catgut was wound tightly over the ends and tied, and then the excess length of the pliofilm was cut off.

Smaller specimens, shown in figure 2, can be sealed quickly if the celluloid ruler is held against the edge of the specimen to protect it and the pliofilm from the heat of the sealing iron. One person can readily seal small specimens, but with large specimens a much neater result can be secured if there is an assistant.

When specimens are kept in a cool place, vapor will coat the inside of the envelope or wrapper, but rubbing the outside of the package will disperse the vapor (which comes from the solution of formaldehyde and helps preserve the specimen). A magnifying glass will enable one to do better sealing by revealing bubbles or defects.

If the pliofilm is overheated it will be damaged; air will have access to the specimen, and seepage will cause hardening of the hands. If a leak occurs somewhere in the envelope, dry the area as completely as possible with cotton. A good blotter will help. When it is as dry as possible, apply a piece of the Scotch cellulose tape.

The work must be performed under a good light. If, in some manner, the specimen eventually shows the effects of air or contamination, take it out of the envelope, keep it in solution of formaldehyde for an hour or more and then reseal in a new envelope.

Dr. Myrtelle M. Canavan, curator to the Warren Anatomical Museum, Harvard Medical School, read the manuscript and made helpful suggestions.

SPECIAL ARTICLES

DIRECT PSYCHOTHERAPY OF CHILDREN

MAXWELL GITELSON, M.D.
CHICAGO

HISTORICAL BACKGROUND

The development and structure of the personality have been in process of elucidation during the last forty years. Many disciplines have participated in this process, but none of them have been so rich in implications for the clinical problems of child psychiatry as psychoanalysis. Freud's basic discoveries need only to be mentioned. His analysis of little Hans,[1] the first attempt to apply these discoveries to the therapy of children, is classic in this field.

It was some time, however, before rational psychotherapeutic work with children was further explored. Outstanding among the early investigators was Hug-Helmuth, whose book [2] appeared in 1921. Contemporaneously, Anna Freud was developing her theories and technic, and in 1927 she published the results of her studies.[3] In 1932 Melanie Klein's book on the psychoanalysis of children [4] appeared. During the last ten years the principles of child analysis have been exerting an increasing influence in the psychotherapy of children in this country, and a number of experiments in the use of modifications and adaptations of the technic have been in process. The present paper is based on experience with such clinical experiments.[5]

THE ROLE OF THE EGO

It is a commonplace, which seems, however, to bear restatement, that to treat the child one must understand him. In medical, and surgi-

Read in part at a meeting of the Illinois Psychiatric Society, Chicago, Oct. 6, 1939.

From the Psychiatric Service of the Department of Neuropsychiatry, Michael Reese Hospital.

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4. Klein, M.: The Psychoanalysis of Children, London, Hogarth Press, 1932.

5. Gitelson, M., and others: Clinical Experience with Play Therapy, Am. J. Orthopsychiat. **8**:466 (July) 1938.

cal practice one does not undertake a therapeutic procedure without a thorough understanding of the anatomic, physiologic and pathologic principles involved. Unfortunately, there is a tendency to assume that the fact of being an adult is *ipso facto* evidence that one knows what is good for the child. Present day knowledge of the structure and function of the human personality has, to a considerable extent, modified this point of view. It is no longer axiomatic that "mother knows best" or that "teacher knows best." Too much evidence has accumulated showing that parental wisdom is often sadly adulterated by tendencies and purposes which have little to do with those of the child. It may be even more regretted that to a large extent the policies of educators, with whom some parents share their responsibility and to whom other parents surrender it entirely, are similarly tainted. This fact, characterizing the conditions under which the infant and child are inducted into adult life, must be looked on as having central etiologic importance in the development of the neuroses of children and adults.

In brief summary, it may be said that the personality develops around the central necessity for managing anxiety. The instinctual tendencies with which the individual person comes into the world are universal and qualitatively similar. There may be quantitative variation in their urgency, based on constitutional differences, but the same instincts are common to all. It is the vicissitudes encountered by the instincts in their development and manifestation that are different. It is the varying intensity of the anxiety generated in different persons by the differing cultural obstacles to their primitive expression and satisfaction that makes for differences. It is the varying technics for controlling anxiety, adopted on the basis of varying identifications and particular talents, that make for differences. This means that the psychologic phenomenon which is called personality finds its individuality in the structure of the ego through which filter the biologic tendencies and their derivatives.

The ego is that part of the personality which is aware—aware of self identity and continuity; aware of bodily tensions and, to some extent, of bodily processes; aware of the surrounding reality and its implications; aware of possibilities for the satisfaction of inner needs and tendencies presented by the various objects in the surrounding reality; aware of the obstacles to such satisfaction, and finally, and most important, aware of consequences. The ego, in short, is oriented chiefly toward reality. In its intermediary position between the world and the instincts, it is able to select and to dose the manifestations of the instincts. The criteria by which it operates to this end come from the milieu. In one home the attitudes toward habit training may be so strict that the feeling *verboten* dominates the life of the child in all other and subsequent relationships. In another home the attitude may be so indulgent that the child never acquires a conception of what inadvisa-

bility, undesirability and inexpediency may mean in subsequent relationships. In still a third home the attitudes may be so vacillating, so unsure, that the developing child never finds out with certainty what is allowed or disallowed, in which directions he may or may not go. In the first instance the consequence may be complete stunting in development, or, on the other hand, the pressure of the ego-alien tendencies (and their derivatives) may be so great that they somehow break through, distorted and disguised by ego-acceptable tendencies. In the second instance infantile omnipotence may continue to manifest itself in those undeveloped personalities which are readily recognized as puerile. Judgment and restraint may be lacking in an astonishing degree, while measurable intelligence as a function of an organically intact nervous system may be contrastingly good. In the third instance one finds developing the typically anxiety-ridden child, who, in attempts to deal with his inner fear and tension, adopts the most varied patterns of aggressiveness and submissiveness: defense by attack or acquiescence, together with varying admixtures of neurotic distortion.

This brings me to the necessity for reviewing certain aspects of the development of the sense of reality which have a particular bearing on the topic of this paper. It is with this function of the personality that the direct psychotherapy of children is most concerned. The material on which this discussion is based is not new. Much of it has been implicit in the past, and pediatric practice is beginning intuitively to follow these implications. The most recent technical restatement and elaboration have been made by Benedek,[6] on whose paper the following section is largely based.

REALITY ADAPTATION IN INFANCY

The original state of the child is one of the so-called "infantile omnipotence" already mentioned. Its sensorium being undeveloped, the newborn child has no perception or conception of itself as a separate entity. Whatever vague type of awareness there is has to do with masses of stimulation which it is known partly arise from the functioning of the body itself. The infant can make no such distinctions. It feels and responds to its feelings in a purely reflexive way. Some kind of tension arises because it is hungry, and that tension, to begin with, expresses itself as a cry. The mother hears the cry and brings either the breast or the bottle. The infant can "know" only that there was tension, that it cried and that "something happened" as the result of which the tension disappeared.

6. Benedek, T.: Adaptation to Reality in Early Infancy, Psychoanalyt. Quart. **7**:200 (April) 1938.

Sometime later the awareness of the infant becomes more finely differentiated. Hunger tension, with its reflex production of crying, becomes connected with the idea of breast food or bottle food. But there is an important consideration here. Observations tend to indicate that the child becomes aware of the mother herself as the agent of release of tension long before the breast or the nursing bottle as such is recognized as the direct agent of gratification. This gradually increasing recognition of an intermediary between cry and satisfaction is the germ of the sense of reality. But it is only the germ. It becomes genuinely an adaptation to reality when the factors of time and expectancy enter in. So long as the cycle is: tension, cry, mother, breast, release of tension, so long is the child still reacting with biologic primitiveness. It is when the cycle becomes: hunger, expectation, mother, food, that one begins to recognize adaptation to reality as it occurs normally in adults. It is the element expectation, with its capacity to hold in abeyance the primitive responses to hunger, which may be looked on as the first manifestation of the functioning of the human ego. When this happens, primitive anxiety response is being adequately kept in check by some awareness of the elements of time and probability.

All this rests on the basis of actual experience. The importance of experience looms immensely large here. It is immediately clear that only to the extent to which experience has been salutary can the capacity for placid expectation develop. It cannot develop without confidence.

Confidence is a new word in the psychoanalytic literature with reference to the psychology of the infant.[6] It is not a completely new idea to those who have been working with children. It has been simply known more vaguely as "security." Security, "confidence," one may say, is that element in the earliest experience of the infant which assures him of the potential kindliness of reality. The first hunger experience can only be one of "awareness" of tension and unmitigated anxiety. Only as anxiety is unfailingly allayed by the appearance of the constellation of the mother and food do confidence and placid expectation develop. In physiologic terms, this is a conditioning process. From the standpoint of the evolution of the total personality it is much more than this. To confidence is attached a capacity to wait. The capacity to wait implicitly carries with it the capacity for awareness of that which is awaited. It means that a non-self is clearly recognized. It means that there is a need and an ability to externalize interest, or to adopt an object orientation in the world.

It is clear that if this development is to occur the conditions for the establishment of confidence must exist in the surrounding world. The security must be there. Only the mother and the home can give this. Uncertain responses to the actual signal of anxiety, disappointments after expectation has been stimulated, these have the inevitable con-

sequence of destroying tentative or established tendencies to react in terms of confidence. The cycle now becomes: tension, expectation with confidence; disappointment; recurrence of the automatic response to tension, namely, crying, and, finally, return or regression to the initial attitudes of omnipotence. To elaborate this somewhat more: Early disappointments undermine feelings of the potential kindliness of reality; the capacity for waiting is weakened; the capacity for directing interest outward toward that which is awaited is depleted. Object orientation is impaired. Introversion occurs, one may say.

Subsequent anxiety tendencies and feelings of insecurity are, to a large extent, to be accounted for on the basis of a real undermining of confidence to begin with. In short, confidence is the feeling of calculability. It is to the experiencing ego a substitute for the primitive efforts to master tension by simple reflex action, such as the cry or the muscular movement of withdrawal. It is the only thing which makes possible the establishment of a harmonious awareness of self and nonself. Out of the mother-child relationship which is harmonious and calculable for the child must develop the capacity for other relationships which are harmonious and calculable.

Parallel and concomitant with the evolution of that aspect of the personality which has to do with the recognition of reality is an elaboration of the instincts which is biologically determined. What happens to these instincts in terms of repression, sublimation, reaction formation, and the like, is to a large extent dependent on the kind of adaptation to reality which the person makes. Later defense mechanisms are more effective and less rigid to the extent that confidence in the external reality assures the person of the most necessary gratifications. The defense mechanisms are less rigid, and the possibilities of distorted manifestations of instinctual pressure are reduced by the pervasive hope and expectation of receiving some degree of satisfaction and indulgence from reality.

To the degree to which the child does not acquire real confidence in the potential benevolence of reality he must elaborate various delusional technics for keeping reality under his control, and thereby safe. The disappointed infant cannot be satisfied that finally the mother does bring food. The food must be served in a certain way. It must be served from the left rather than from the right. The mother must pick up the child in one way and not in another. Notwithstanding the pervasive fact that the mother herself means security, no matter what other modifications there are in the situation, the compulsive need develops to manage the details of the situation without regard for the unity with the mother. The person remains fixed to rigid conditioning factors rather than in a situation of free adaptability under the protection of the one important factor, confidence.

Confidence in the essential benevolence of the surrounding reality, because it liberates the person from the most pressing source of anxiety, danger to his very life, frees him to turn energy which would have been otherwise consumed by anxiety in other directions, namely, toward learning in the more intellectual sense. It leaves more energy for observation of objects and their relationships and for experimental manipulation of relationships. It gives courage for taking each necessary new step in actual learning because, in its simplest terms, courage is confidence that there is a safe place to return to if necessary.

This does not mean that the instinctual tendencies are completely dealt with on the basis of security in the relationships to the external world, as discussed thus far. What it does mean is that such security makes it possible for the person to come to an equitable agreement with reality. This is the element of calculability which I have mentioned. It is an awareness of causal relationships, of the possibility of compromise, of the fact that there is not only renunciation but also indulgence.

The inhibitory influences to which the child of necessity must be subjected are more tolerable, are more acceptable, to the extent to which general security, with its promise of partial indulgence, prevails. For confidence is a prerequisite to a belief in justice; it is a prerequisite to a belief and expectation that one will be left at the mercy neither of a dangerous reality nor of unrelieved instinctual pressure. When infantile confidence, in the sense in which I have discussed it, has been lacking, every new anxiety situation results in the return of the old insecurity, of the old feeling of helplessness. The timidity and withdrawal and the stunted ability to learn and capacity for self respect which many children show are manifestations of the lack of a successful experience in obtaining relief from anxiety and tension in the earliest contact with reality.

In the actual situation what does all this mean? One must turn to the feeding situation for the answer. Too much of this aspect of the early rearing of the child has been conditioned by intellectual consideration of what is hygienic rather than by the facts of emotional development of the child. Too much rigid ritual has been established about the idea of the importance of fixed periods of feeding. Too early the attitude is adopted, with medical approval, that the infant from the beginning must be compelled to meet external standards. Too often these external standards play into the neurotic or culturally determined attitudes of mothers, for whom it is more convenient to believe that a three or four hour schedule of feeding is more important than a flexible response to the particular life rhythm of the child. The bogey of spoiling rears its head too early. The infant is not given a sufficiently long period of transition from the constant nutritional state of the uterus to the final periodic nutrition of the adult. The anxiety and bodily

tension, and even pain, from which a child suffers who is subjected to an externally imposed rhythm not consonant with its own needs is the actual basis of the insecurity and the lack of confidence which I have described.

THE TRAINING EXPERIENCE

There is another aspect of the relation of the child and the mother which must be further elaborated. In addition to problems of actual biologic security, the expanding awareness of the child is confronted by inhibitory influences representative of the culture into which he must fit and of which, to begin with, the mother is largely the protagonist. More and more the child's recognition of expediency grows. The question "What is satisfying and at the same time safe?" becomes the content of his emotional preoccupations. Assuming that a child's primitive feeding needs as individually determined have been met, emergence of the other instincts introduces new problems of adjustment. Even normal development is attended by the anxieties attached to this and is connected with various fantasies of possible retribution, such as loss of love and necessary care, or of actual physical injury. The normal child, under the care and guidance of stable parents, builds up a picture of the demands of reality which is stable, and with this as a frame of reference it is possible for him to make a harmonious reconciliation between his instincts and external demands. It is the child provided with a distorted or shifting frame of reference by neurotic parents, who have themselves had a similar experience, who becomes burdened with anxiety. He is neither primitively free to relieve instinctual tension nor able to discern with certainty on what external renunciations and compromises his security depends. A mother's attitude toward her child is influenced by her own emotional adjustment to her mother or father. The mother's emotions will, as they emerge in relation to the infant, contain her whole past. The woman who has strongly repressed or denied her own instinctual life will, in her own person, recapitulate the forces that induced this in her, and her child will be subjected to the same forces. She is afraid of anger or sexuality in the infant because she fears these in herself. The child's fears of his own aggressive and erotic impulses are reflections of his awareness of the mother's fear of these in the child and in herself.

Particularly important are the oscillation of attitudes and distortions of truth to which neurotic mothers expose their young children. To use a colloquialism, children from such a setting "don't seem to know whether they are coming or going." On the one hand, they have been indulgently and seductively treated, but, on the other, they have been unsatisfied in their profoundest needs and have been forbidden their most natural outlets. They have had no opportunity for making a stable identification. Their self esteem has been undermined by atti-

tudes which never gave recognition to their spontaneous capacities, tendencies and directions. They have always been intrinsic emotional aspects of the parents' own lives rather than individuals aware of their own prerogatives as well as those of the parents. It is not mere ignorance or error which is involved. The children of the primitive peasant woman may present all of the problems which a faulty social-cultural milieu will breed, but they are not thereby neurotic. Such a mother may have lashed out during momentary anger, for instance, in a manner unthinkable for a cultured mother. The point, however, is that in the former case the child can recognize the causal justice of such an outburst. He is aware of the role which he, as a momentary irritant, has played in producing it. The assurance that the reaction is determined by a specific interpersonal transgression leaves his essential security undisturbed, while the well behaved, undifferentiated resentment of the second mother has a devastating effect.

THE THERAPEUTIC PROCESS

This brings me to the question of psychotherapy. Its purpose may be twofold. On the one hand, it may be directed toward correcting the environmental-emotional conditions under which the neurotic child has developed. On the other, one may undertake a systematic reconstruction of the internally crystallized pathologic tendencies.

The latter procedure is child psychoanalysis. It is the procedure of choice in cases in which the child's defenses have become structuralized, as they do in the neurotic adult. As a matter of fact, to a certain extent, every so-called behavior problem represents such structuralization. To the extent to which this is true, analysis is the only procedure which will be effective in the sense of actual cure. Such specific problems as recurrence of enuresis after the original acquisition of control, tics, compulsions and obsessions and specific phobias can be treated etiologically only by "systematically revealing hidden meanings at dynamically specific moments," as Homburger has said.[7] However, psychoanalysis is not always available or feasible. Besides, large numbers of children are brought to the clinics whose fundamental problems lie in a disturbed adjustment to reality in the sense already discussed. Even if specific neurotic symptoms are present, the environmental influences which have contributed to their origin and now sustain them cry out for intervention. Here a corrective procedure find its indication. What follows is an elaboration of this procedure.

Corrective psychotherapy is an aspect of treatment which is applicable and helpful under the conditions of ordinary clinical practice. It is treatment which the child psychiatrist is called on to give in order to

7. In discussion on "Play Therapy" (1938), Am. J. Orthopsychiat. **8**:499 (July) 1938.

eke out the lacks in the existing educational systems and personnel. It is treatment which the psychoanalytically trained psychiatrist can most safely apply because he must be prepared to evaluate and circumvent the danger which even an educational procedure must encounter.

When I speak of correcting and changing the emotional-environmental conditions under which the neurotic child has developed, it is clear now that I have reference to the interpersonal experiences of the child from birth. One is concerned with the effect of the impinging attitudes of parents and teachers on his biologic tendencies. These tendencies have their normal direction and mode. Their final expression is a compromise between their own urgency and the counterpressure of the denials and allowances of the surrounding reality. Their harmonious development is dependent on the certainty of balance between indulgence and denial. In the neurotic home this does not exist. The outstanding characteristic of the emotional environment of the neurotic child is its chaos. The ambivalence of the affects and the delusional or insincere intellectual attitudes of the adults give the child no anchorage and no goal.

Placement in foster homes is the classic procedure for directly modifying the emotional environment of the child. In cases in which the child's own home situation is manifestly untenable the indications are clear. The difficulties are with the coexisting contraindications. For instance, frequently after the decision to remove a child from an exceedingly bad home, one comes aganist the baffling fact that the child will not leave the home, or that if he does he will return to it, or his neurotic symptoms will increase. At any rate, the rationale of the attempted treatment is evident. If the home influences are bad, whatever the theoretic concept in the case, all will agree that a good home is the solution. The problem is: What is a good home for the particular child? And when one has arrived at an idea of that, where can it be found? This goes beyond the topic of the present paper.

However, one is left with that large group of neurotic children who do not come from homes in which the indications for removal are compelling. Given such a child, who has not too completely structuralized his anxiety in the form of severe neurotic symptoms or character traits, that is, given a child presenting a behavior problem who has reacted to adverse influences by means of defensive inhibition or withdrawal or, on the other hand, by attempts to regain security through various aggressive attempts at domination and mastery, one can hope to secure significant improvements in his happiness and social adjustment by a corrective or reeducational therapy the central feature of which is that the patient reexperiences himself in a non-neurotic setting, or, as one may say, reconditions his impulses and tendencies in terms of a more reliable system of signals than those provided by his parents and educators.

What is required is the assurance to the child of the existence of love and security as a pervasive fact which only important transgressions can jeopardize.

It must be seen now that the problem of treating the child, even "correctively," at the level of his conscious, experiencing awareness is not insignificant. It is as important and far reaching in its implications as was the original problem of rearing him. It is more difficult because the therapeutist does not start with the fully plastic material which is the newborn child. From the beginning of therapeutic contact, he is confronted by far reaching attitudes of distrust and fear, rooted in early and often repeated disappointments of needs and dislocation of goal. He cannot hope to begin therapy without getting inside the guard of the child. He cannot do this without establishing the child's confidence in him. He cannot accomplish this if his own feelings about himself and the personalities of others are as yet uncertain or if the conditions under which he works do not insure steadfastness and continuity in his relationship with the child that make for the "confidence" I have already discussed.

The therapeutist must therefore be a person whose own view of life is clear and whose adjustment is secure. Unresolved anxieties in the therapeutist are bound to reveal themselves as they did in the parents, and children are especially capable of becoming aware of this. More necessary even than in treatment of the adult are a deep interest and capacity for valuing the patient as a person apart from his scientific interest. With notable exceptions, this capacity, in my experience, is more generally found in women than in men. There are certain individual technical considerations which present positive indications for the choice of a therapeutist of a given sex. For instance, at the beginning of, or at certain stages in, the treatment of a boy with enuresis it may be advisable for him to have a male therapeutist. However, by and large, there seem to be more women than men who have the intrinsic capacities which seem most necessary in the treatment of the child.

The child therapeutist is from the first responsible for instituting the treatment of the patient. Adults who come for treatment have more or less insight into their sickness. They themselves are asking for some kind of help. Most neurotic children, except those who come under false impressions created by the parents, have no personally accepted reason for dealing with the psychiatrist. Their symptoms, if of the acting-out type, are well rationalized. If the child actually suffers from an anxiety or inhibition, the causes are completely projected, and the psychiatrist is just another person in the world at large. Of necessity, then, the prospective therapeutist must be active in winning a positive attitude from the child. Sometimes the balance in the therapeutist's own personality is sufficient for this. It becomes manifest to the child that here is a

secure person, a stable person, a different sort of person than those whom he has known before. Sometimes the psychiatrist must go through a period of being on trial, of being tested, of demonstrating in the actual new experience of the child that here is one adult who is less forbidding, less dangerous, less vacillating, less unreliable than other adults have been. This does not mean that an obvious and overt display of emotion is needed. Too often the child has already experienced such manifestations and has learned to distrust them. What is important is what the therapeutist actually feels and is, not merely what he is capable of acting like because of his ethical strivings.

With a particularly defensive and unresponsive child, the psychiatrist's insight into the unexpressed emotional disturbance of the patient may be communicated to him in a way to indicate that here is an adult who realizes something about him that is really important; some one who offers promise of understanding things in a different way than guardians or teachers do. This does not mean that the child must feel that here is a person who, seeing his instincts and impulses pressing for expression, will permit them full sway. Children who, for internal reasons, have this feeling or who, through technical error, acquire it, are quite likely to run away from the therapeutist soon or to develop difficult defensive attitudes. On the other hand, the therapeutist cannot appear critical, punitive or categorically forbidding. Paraphrasing an expression of Anna Freud,[8] one might say that the psychiatrist's position with reference to the child's tendencies needs to be: "not at this time" or "not in this way," rather than a categorical "don't," or, on the other hand, a libertine blanket freedom. What the neurotic child needs is that the adult should "represent to him a stable ordered world of values,"[9] which, however, are adjusted to the level of his instinctual and emotional development as one finds it at the time. There are periods and moments in the child's life in which it is normal for him to be destructive or erotically self exploratory. However, children need to feel that adults are stronger than they, but this in the sense of an orderly reality rather than of a destructive threat. The child must know that the adult to whom he gives his dependence is able to manage his impulses for him when necessary, because these impulses themselves are capable of creating an inner fear of retaliation which may be as bad as or worse than the momentary surrender of them. In short, the therapeutist must give the patient one constant point of reference in what, for him, has previously been a chaotic world. This concerns not only the child's needs for dependence but also the necessity for

8. Freud, A.: Psychoanalysis and the Training of the Young Child, Psychoanalyt. Quart. **4**:1 (Jan.) 1935.

9. Isaacs, S.: Social Development in Young Children, New York, Harcourt, Brace & Company, Inc., 1937.

calculable and predictable standards of conduct, which, while they are permissive, are also delimited.

The vehicle of the relationship between the child patient and the psychiatrist is play. Unfortunately, the misleading term "play therapy" has attached itself to this. Play, as such, is therapy only in the same general sense that eating is therapy. The child must play if he is to make the necessary abreaction of his normal physical tensions. He must play if he is to develop the courage, initiative and sensorimotor skills which adult life will demand of him. But, in the technical meaning of therapy, play itself is not treatment. Simply turning a neurotic child loose in a roomful of toys will not serve the purpose of treatment.

Play is the language of the child.[10] Long before he acquires adequate verbal facility to express the nuances of his impressions and reactions he is acting them out in his play. Not only is play meaningful in terms of symbolization, but its general character and its timing have dynamic significance. Like the dream, it is eloquent about things, people and situations and their relationship to the central figure, the playing child. As in the case of the dream, psychoanalysis has taught the language of play.[11]

A boy aged 6, each time that he comes into the treatment room, asks if there is "anything new" there. Not only does he inquire but, with great thoroughness, he searches the room. It is useful to understand that his neurotic difficulties began when his mother, unannounced, brought home the new baby. "Anything new" is "anything" like the younger sibling, whose arrival ushered in great resentment and consequent anxiety. The child's behavior has told rather completely what he had no words to express. A garrulous adult might have concealed more.

Play, then, has the significance of catharsis and confession, as speech has for the adult. One does not, however, refer to the interview with the adult as "speech therapy." Therapy is what the therapeutist himself does and says in response to the patient's communications. Sometimes he is silent; he simply lets the patient "talk it out." The same is true with the child. Sometimes, in the presence of the therapeutist, with the tacit implications of his significance as such, the child is simply allowed to "play it out." But even the passivity in such a case is elective and follows an indication. It is this last which is really the therapy.

For the most part, one is not so "passive" with the child. As Helen Ross has expressed it,[7] one wants from the child "as free play as pos-

10. Lowenfeld, M.: Play in Childhood, London, Victor Gollancz, Ltd., 1935.

11. Homburger, E.: Configurations in Play: Clinical Notes, Psychoanalyt. Quart. **6**:139 (April) 1937. Peller, L. E.: The Child's Approach to Reality, Am. J. Orthopsychiat. **9**:503 (July) 1939.

sible so that the play has meaning" (particular to the given child). Too scrutinizing a "side-line" attitude will defeat one's purpose to obtain this. Too much participation, either physically or emotionally, makes it difficult to make evaluations of what the child himself is feeling and expressing. The therapeutist usually permits the patient himself to decide how much participation there shall be, but remains in control as regards how far it shall go. A child who is venting his resentment toward a member of the family would not be allowed to strike the therapeutist as a surrogate. Though his emotion would not be criticized or forbidden, it would be diverted. A pillow or a doll may be interposed if the therapeutist is quick enough. In any case, overt aggression would be prevented. This likewise applies to destruction of equipment which cannot easily be replaced and which is for general use in the treatment room. Nearly everything else "goes" and is dealt with in terms of its implications rather than of its content. The therapeutist may from time to time be given various roles to play. He accepts these roles, but his general purpose is to let the child write the entire script, and the comments he introduces are directed toward cultivating the patient's own elaborations.

Of course, the child talks while he plays. Not everything is dependent on the understanding of the implications of the bodily activity and on the manipulation of toys. The closer the relationship of the child and the therapeutist becomes, the more confidence the child develops, the more he is able to assume the responsibility for expressing himself directly in words. In some phases of the treatment situation the child may communicate entirely by word of mouth, and only when excessive anxiety develops will he retreat again to the less direct revelations which he makes through his play. At other times the play may be for its own sake, especially when a particular problem has been solved and the patient, for the time being, is simply using the companionship of the therapeutist as any child might. Periods of "reading together" most often represent this.

The aim is to help the patient follow through within himself those feelings and attitudes which are inhibited in their expression, though not repressed. It is then the task of the psychiatrist to help the child to a rational reevaluation of them. Much of this goes on tacitly, by virtue of the permissiveness, understanding and relaxation of the therapeutist's attitude toward what the child is revealing. But to a greater or lesser extent the therapeutist must make specific statements which are oriented toward the same end. Such statements can, in this type of treatment, only be loosely termed "interpretations." As I have already indicated, "interpretation means revealing hidden meaning." This is possible, useful and generally permissible only in an actual analysis. In the more superficial type of psychotherapy which I am

discussing, the psychiatrist's comments are really didactic, enlightening, permissive and rationally controlling. They are therapeutic because of the setting of emotional justice in which they are made. The child learns through these so-called interpretations that he is not alone a wicked vehicle of resentment and aggression and that the erotic tensions and impulses which he experiences are not particular personal devils. This is the "reconditioning" situation which was alluded to previously.

It is worth while to quote Homburger again.[7]

> One is not interpreting if one tells an aggressive child . . . that he seems to be angry with some one, or assures an inhibited child who still shows a conscious conflict about touching dirt that sometimes it is fun to play with dirt. [With such statements] . . . , one merely shows the child that one recognizes [and is willing to admit the existence of] infantile impulses. This is an important therapeutic measure which is indispensable in child psychotherapy and in the preparatory stages of child psychoanalysis.

It is this phase of child rearing and child education that is defective. It is because parents and pedagogues, unable to recognize or accept their own infantile impulses, will not deal with their children in terms of the reality of their existence that the child psychiatrist is, at a later and less propitious moment in the life of the child, compelled to take over this task for them. Unfortunately, too many neurotic children have then progressed beyond the point of being significantly aided by less than prolonged analytic treatment.

The aims of the child psychiatrist during the course of treatment may be summarized as follows: (1) to decrease the feeling in the child of being exceptionally or irretrievably bad; (2) to introduce an attitude of self tolerance with regard to anxiety arising out of conscious hostile, aggressive tendencies and to attempt to show the patient that some of these tendencies have a natural sanction in the situations in which they arise; (3) to supply lacking information at propitious moments when the child's anxiety comes from obvious ignorance; (4) to clarify where possible conscious conflictual relationships in the immediate life situation; (5) to dispel, through the influence and new example of the psychiatrist himself, as a stable, reality-oriented personality, the delusional conceptions of human beings and their relationships which neurotic parents engender; (6) to point the way to compromises with realities which are inevitable. By this is meant that the child, after all, must live during and after the treatment in a neurotic environment. This is the outstanding reality. The psychotherapeutist needs to work through with the child the fact of the difference between the treatment situation and the environment. The child must be taught that the sense of inner freedom which the therapeutist helps him to acquire in relation to himself can continue to be a criterion for his emotions but not for his overt acts.

From the point of view of the child, the effect of such treatment has been lucidly stated by Dr. Margaret Gerard:[7]

> There is no question in my mind but that the free play in which the child indulges in cooperation with an adult has certain values beyond the free play which he indulges in with other children. In other words, he learns to realize that all adults do not offer the same taboos, have not always the same standards of behavior which his parents have, and is able to express tendencies which he has not been able to express in the presence of adults at home. [This] enlarges his capacity for action in the reality situation. He experiments . . . with his freedom, and thus extending his activity, we get what we may call a real ego change.

This change in the child's view of himself and of the world around him makes his relationships with others more placid, and his sublimative and pedagogic capacities are correspondingly improved.

As has hitherto been implicit, the minor (but not insignificant) psychotherapy described in this paper is based on the major undertakings of child analysis. In the main, the clinical and theoretic principles of Anna Freud's work are followed. Her theories of the structure of the child's ego and its needs, unlike those of Klein, are more clearly inferred from the material available for study under the usual conditions of a child guidance clinic. The derivatives of her principles, also, are more easily applied under clinical conditions, in which the demands for help are pressing and child psychoanalysis is out of the question.

CLINICAL EXPERIENCE

As has been said, work of the type described here has been evolving in the children's clinics of the United States during the past ten years. It has significantly enriched the classic child guidance program. Four years ago, I initiated the method at the Institute for Juvenile Research, at Chicago, where it has been continued as an important phase of the work of that clinic. Unfortunately, not many statistical reports are as yet available. In July 1938 I published a preliminary analysis of the work in the first 40 cases.[5] Twenty of the children were treated exclusively according to the principles described here. Of these 9 showed significant improvement. The other 20 children received collateral treatment, such as placement in foster homes or school adjustments. Of these, 15 improved. It must be noted, however, that in the latter group 5 children had previously failed to respond to classic child guidance procedures alone. It would seem, therefore, that in these cases psychotherapy through the medium of play was of determining significance.

Such a small total number of cases does not permit final conclusions. However, the prognosis for some of the children who showed improvement would have been poor had this therapy not been available. Moreover, treatment of some of the children who were classified as not improved failed because of unmanageably bad external conditions.

Nevertheless, one cannot look on direct psychotherapy of children as a completely self-sufficient procedure. The external obstacles cannot be overlooked. Untenable home situations, specific educational defects, the unconscious sabotage of well intentioned but neurotic parents must be dealt with. It is not infrequent that failure to work successfully with emotional problems of the mother spoils the results with a child who by himself would have progressed to a satisfactory outcome. Treatment in such instances requires the closest collaboration of the psychiatrist who is working with the child and the person who is dealing with the home and the school. The results obtained in such instances are expressive of the interdependence of direct psychotherapy and the therapy of the milieu.

Finally, it is necessary to repeat that psychotherapy of the child is not merely "free play" in the presence of any kindly adult. Transference and catharsis certainly operate in the treatment, and these are in some cases the principal factors in healing. However, one cannot forget that in the permissive, secure atmosphere of the treatment room, positive instinctual strivings variously modified by dependency needs, envy, resentment and fear come into play. These must be understood as forces in a dynamic process the operation of which is governed by definite psychologic laws. Psychoanalysis has precisely defined these laws. One must know and be sensitive to them to conduct even superficial psychotherapy with children.

DISCUSSION

DR. GEORGE J. MOHR, Chicago: This paper by Dr. Gitelson is a particularly clear discussion of a topic difficult to present. Dr. Gitelson confined himself to treatment of children not deeply disturbed, and I should like to emphasize the role this type of therapy plays in efforts to help children. Often when placement is secured in a suitable foster home, the environmental change seems to have little effect in improving the situation. The disturbing reactions persist despite this change. This difficulty is encountered with children who have acquired established patterns of behavior, which reveal their feelings of resentment or discouragement and anxiety. These reactions, of course, arise as a result of frustrating experience. Even when the child is placed in a potentially satisfying environment, the old behavior persists or quickly recurs when he is once established in the environment. The type of therapy Dr. Gitelson has described offers the child an opportunity to accept a relationship with the therapeutist free from the resentful reactions induced by earlier thwarting experience. This offers the bridge to the establishing of good personal and social relationships with others in the new environment.

News and Comment

AWARDS FOR OBSERVATIONS ON EPILEPSY

Two annual awards of $100 each are offered by the Laymen's League Against Epilepsy for the best original unpublished observations or investigations bearing on the subject of epilepsy. One of these is for work done in a state colony for epileptic patients or in a state hospital for patients with mental diseases; the other is for work done elsewhere. Since one object of the award is the encouragement of junior workers, the committee will take into consideration the facilities of the authors; clinical as well as laboratory studies will be welcomed. Awards will be made by a committee of three, composed of the president of the American League Against Epilepsy, the chairman of the Section on Convulsive Disorders of the American Psychiatric Association and a physician chosen by the officers of the Laymen's League Against Epilepsy. It is hoped that winning contributions will be presented before the annual joint scientific session of the first two of these organizations. At the discretion of the committee, awards may be divided or postponed.

Contributions for 1940 should be submitted by December 15. Further information can be obtained from the secretary of the League, Mrs. N. Bond Fleming, 25 Shattuck Street, Boston.

COURSE OF INSTRUCTION IN THE RORSCHACH METHOD OF PERSONALITY STUDY AND CLINICAL DIAGNOSIS

A course of instruction in the technic of administering the Rorschach test, scoring the responses and interpreting the results will be given by S. J. Beck, Ph.D., head of the psychology laboratory of the Michael Reese Hospital, Chicago. Especial emphasis will be placed on clinical classification. Records of responses obtained from various groups representing healthy personalities and from clinical groups (including patients with schizophrenia and some neuroses) will be scored, analyzed and interpreted. The primary aim of the course will be to demonstrate the practical application of the test in investigating the whole personality, with particular reference to its clinical use. The course will be presented in two two hour sessions daily for five days, June 24 to 28, 1940, inclusive. Persons interested are invited to communicate with the medical librarian, Michael Reese Hospital, 2908 Ellis Avenue, Chicago, for further information.

Abstracts from Current Literature

Anatomy and Embryology

EPISCLERAL GANGLION CELLS. ISADORE GIVNER, Arch. Ophth. **22**:82 (July) 1939.

Givner studied the ciliary ganglion in serial sections of 10 eyes in unselected cases. Ganglion cells were found in every eye situated usually with a ciliary nerve, sclerally, episclerally or a short distance from the globe near the optic nerve.

SPAETH, Philadelphia.

AN EXPERIMENTAL STUDY OF THE RELATION OF SENSORY CONTROL TO MOTOR FUNCTION IN AMPHIBIAN LIMBS. PHILENA EVANS CHASE, J. Exper. Zoöl. **83**:61 (Feb.) 1940.

The developing forelimbs of embryos of Amblystoma punctatum were deafferented by excising the brachial neural crest before or during the migration of the crest cells (stages 19 to 29), or by removing the brachial ganglia as soon as they appeared as discrete masses (stages 39 to 45). Movements of these limbs were studied later in relation to the quantity of sensory fibers which could be traced into the corresponding brachial plexuses. In most cases there was a close correlation between the amount of afferent innervation and the extent of motor activity in the larval forelimb.

Nerves of both forelimbs and hindlimbs of adult specimens of Triturus viridescens were deganglionated. Coordinated use of the limbs was not immediately affected, but after six weeks there was hyperextension, which became progressively more severe. The evidence indicates that afferent innervation is significant in the building up of motor patterns in urodele limbs, but that such motor patterns when once established are not destroyed by deafferentiation.

WYMAN, Boston.

INTRACEREBRAL DISTRIBUTION OF ARTERIES ORIGINATING FROM THE MENINGEAL VESSELS. N. BERKOL, A. MOUCHET, Z. ZEREN and M. OYA, Ann. d'anat. path. **16**:861 (July) 1939.

Roentgenograms were taken of brains which had been injected with a radiopaque substance. It was found that two types of vessels arise from the meningeal arteries, short ones (*griséo-corticales*) for the gray matter and long ones (*albo-corticales*) for the white matter and the subependymal tissue of the lateral ventricles. The arteries of the first group are arranged in parallel formation perpendicular to the surface and measure about 2 mm. in length. More than forty of these were counted in 0.5 cc. of tissue. The arteries of the second group are larger, but less numerous. Their length varies in different regions, reaching 40 mm. in the frontal and occipital lobes. Those arising at the free surface are longer than those originating in the depth of a sulcus. Their collaterals are apparently small, since they could not be demonstrated in the roentgenograms. The arteries of the white matter are terminal.

WEIL, Chicago.

RELATION BETWEEN THE DEVELOPMENT OF MYELIN IN THE OPTIC NERVES AND THAT OF THE VISUAL SENSE. DENKISHI MISHIMA, Ann. d'ocul. **176**:304 (April) 1939.

Mishima reports that myelin of the optic nerves is visible between the twenty-fifth and the thirtieth day after birth and is completely developed between the thirty-fifth and the fortieth day. The pupillary reaction occurs from the thirteenth

to the fourteenth day. The myelin of the ciliary nerves and of part of the fibers in the central area of the optic nerve is formed earlier than the myelin of other orbital nerves.

BERENS, New York.

THE INNERVATION OF STRIATED MUSCLE FIBERS. ERIK AGDUHR, Upsala läkaref. förh. **45**:399 (Oct.) 1939.

This study was undertaken to demonstrate the multisegmental innervation of single muscle fibers and nerve-ending organs. Agduhr studied sections of the interossei and lumbricales muscles of the anterior limbs of the cat impregnated with silver according to the method of "optic sectioning in series." He observed muscle spindles with monosegmental, bisegmental and even trisegmental sensory innervation and monosegmental and bisegmental tendon spindles. He saw single muscle fibers with multisegmental motor innervation. There were muscle fibers with two motor end plates from the same segmental nerve, but probably from different anterior horn cells. There were also muscle fibers with two motor end plates from a single anterior horn cell. One of these end plates as a rule was very small, with a thin efferent nerve branch. Agduhr observed that when different motor plates from different neurons are located in a single muscle fiber one of the end plates is larger than the others. This study was undertaken to refute Wilkinson's criticism of Agduhr's similar earlier claims.

NOTKIN, Poughkeepsie, N. Y.

Physiology and Biochemistry

A STUDY OF THE EFFECT OF RIGHT FRONTAL LOBECTOMY ON INTELLIGENCE AND TEMPERAMENT. T. LIDZ, J. Neurol. & Psychiat. **2**:211 (July) 1939.

Lidz investigated the effect of right frontal lobectomy on intelligence and personality in the case of a highly intelligent man with a slow-growing oligodendroglioma. The tumor produced few clinical signs other than infrequent episodes of unconsciousness, making the case especially suitable for this study. The entire right prefrontal region up to area 6 of Brodmann was excised. For several days after operation diminution of the normal drives, difficulty in initiating speech and compulsion to count things were noted, but these signs gradually disappeared. There were no physical symptoms other than a slight increase in the deep reflexes of the left extremities. The patient was subjected both before and after the operation to the following battery; the revised Stanford-Binet test; Cattell test, scale III; the McCall intelligence test; Kohs block design; the Porteus maze; Thurstone samples; Burt's graded mental arithmetic and reasoning problems; a variety of tests for memory and mental grasp, and the Downey will temperament test. With the exception of minor changes, the results in all instances indicated that the lobectomy produced no modification of intellectual or personality functions. There was no evidence of deterioration in the ability for abstract performance, as described by Goldstein. The present case confirmed in the main the conclusions reached by other authors concerning the absence of definite mental deterioration following right frontal lobectomy.

MALAMUD, Ann Arbor, Mich.

THE REACTION OF THE PIAL ARTERIES TO SOME CHOLIN-LIKE AND ADRENALIN-LIKE SUBSTANCES. V. LUNN and M. FOG, J. Neurol. & Psychiat. **2**:223 (July) 1939.

Lunn and Fog investigated the effect of epinephrine-like and choline-like substances when injected into the pial arteries of cats. They found that epinephrine-like substances produced vasoconstriction, but only in vessels larger than 50 microns in diameter and that choline-like substances produced vasodilatation in vessels larger than 30 microns. The smaller arterioles and capillaries remained unchanged.

Of the vasoconstrictor chemical agents used, namely, epinephrine, paraoxyphenylmethylaminoethanol (sympatol), betaphenylisopropylaminosulfate (mecodrin) and its derivatives, sympatol produced the most pronounced constricting effect. Of the vasodilator substances used, namely, acetylcholine, carbaminoylcholine chloride (doryl) and mecholyl, doryl was the most effective. In general, the dilatations were more prolonged than the vasoconstrictions. On the basis of previous experiments the authors suggest that the chemical stimulation by these drugs may be considered identical with electrical stimulation of the nerves to the pial arteries.

MALAMUD, Ann Arbor, Mich.

RETINAL ARTERIAL TENSION IN CASES OF INTRACRANIAL TUMORS: ITS IMPORTANCE FOR TOPOGRAPHIC DIAGNOSIS AND ITS ROLE IN FORMATION OF CHOKED DISK. G. DE MORSIER, M. MONNIER and E. B. STREIFF, Rev. neurol. **71:** 702 (June) 1939.

De Morsier and his co-workers review the evidence in 21 cases of intracranial tumors, verified as such surgically or at necropsy, in order to determine the significance of cerebral tumors for retinal and spinal tension and the formation of choked disk. The age of the patients ranged between 11 and 60 years. The authors established two indexes: a retinohumoral tension index, obtained by dividing the normal diastolic retinal tension by the normal diastolic humoral tension of the 21 patients, and a retinospinal tension index, ascertained by dividing the retinal tension by the spinal tension. Methods of measurement and arithmetic results are indicated. The authors found (1) that, contrary to accepted views, intracranial tumors were accompanied much more frequently by retinal hypotension or normal retinal tension than by retinal hypertension (only 6 of the 21 patients [28 per cent] had retinohumoral hypertension, 12 had hypotension and 3 had normal tension); (2) that the retinohumoral tension index unmistakably indicated variations according to the site of the cranial tumor, with greater retinal hypertension accompanying tumors in the posterior cerebral fossa (except in 2 cases). From these observations the authors deduce that factors other than compression of the brain are productive of retinal hypertension (frequently observed, e. g., as a sequel of craniocerebral traumas). Retinal tension may well be conditioned by disturbances in the control centers of cerebral vasomotricity. In their study of retinospinal tension in relation to choked disk the authors were led to formulate the following observations: 1. The retinospinal tension index is not affected by the position of the tumor. 2. A certain connection exists between spinal tension and formation of choked disk, papilledema invariably arising when the spinal tension rose to 80 mm. or higher but capable of developing with a spinal tension as low as 40 mm. 3. Choked disk appeared (with 2 exceptions) when the retinospinal tension index fell below 0.58 (less than half the normal index of about 1.2). The authors think that these observations which they admit need to be studied more extensively, have interpretative significance for noncerebral tumors. They point out that choked disk is much less frequent in cases of intracranial tumors than is generally assumed. The low frequency (in 8 of 21 cases, or 38 per cent) is ascribed by them to the regular employment of encephalography.

J. A. M. A.

NORMAL BIOELECTRIC MANIFESTATIONS IN THE HUMAN BRAIN. A. E. KORNMÜLLER and R. JANZEN, Arch. f. Psychiat. **110:**224 (Aug.) 1939.

Electroencephalographic observations on animals and human beings have led Kornmüller and Jansen to the following conclusions: 1. From a given point on the scalp, within relatively narrow limits, one can obtain differences in potential referable only to that part of the cortex which lies directly beneath it. Because of this, when one uses fronto-occipital leads it is possible to obtain bioelectric activity only of these two regions. These findings contradict the contention of Adrian that an occipital focus can spread its influence over a large area on the

scalp. 2. As a corollary to the preceding, it is necessary to assume that in the cortex there is a definite differentiation of bioelectric activities. When gross differences in frequency are taken as criteria, the distinction between specific bioelectric manifestations is not easily recognized. One must also consider the form of the resulting waves. In this way, through combined characteristics of frequency, amplitude and form, the electroencephelographic records may serve as useful indicators of normal or disturbed cortical function in different parts of the brain.

MALAMUD, Worcester, Mass.

CREATINURIA IN DEFICIENCY OF VITAMIN E AND ITS CURE BY DL-ALPHA-TOCOPHEROL (SYNTHETIC VITAMIN E). F. VERZÁR, Schweiz. med. Wchnschr. **69:** 738 (Aug. 19) 1939.

Verzár says that creatine or creatinine not only originates in endogenous muscular metabolism but is taken in with the food, and some investigators maintain that it derives also from arginine. Creatinuria is observed not only in disturbances of the glycogen metabolism of muscles but also in some endocrine disturbances. It has been observed in connection with hyperfunction of the anterior lobe of the hypophysis, with pregnancy and with hyperthyroidism. Moreover, in animals the administration of anterior hypophysial preparations and of "sex hormones" (androgen and estrogen) has been known to produce an increase in the elimination of creatine and a decrease in that of creatinine. Postclimacteric creatinuria has been suppressed by the administration of androgen. All these observations indicate that creatinuria may be elicited by reduction in the production of "sex hormones" or by disturbances in the anterior lobe of the hypophysis. New light was thrown on the problem of muscular dystrophy by the observation that certain diets elicited muscular dystrophy, but that they failed to do so when they were complemented by wheat germ oil, with its high vitamin E content. The author cites his own observations on the creatinuria of rats with muscular dystrophy, which were fed for a number of months a diet lacking vitamin E. He further shows that it was possible to counteract the creatinuria of animals with muscular dystrophy by means of a synthetic vitamin E (dl-alpha-tocopherol acetate). He found that whereas the daily administration of 50 mg. of this synthetic vitamin E produced some effect in the animals, 200 mg. daily was required to produce normal creatine values. The large quantities of synthetic vitamin E that are required for cure are surprising, because only small quantities of vitamin E are necessary to achieve a prophylactic effect. Experiments with synthetic vitamin E revealed that it effects fixation of creatine but that this fixation ceases as soon as does the administration. Regarding the point of attack of vitamin E in the organism, the author says that in 1930 he advanced the theory that it is in the anterior lobe of the hypophysis. He summarizes his discussion by stating that creatinuria is a result of disturbance of the muscular metabolism, on the one hand, and of the reduction of the secretions of the anterior lobe of the hypophysis and of the sex glands, on the other. The function of these two systems is impaired in case of deficiency of vitamin E. The administration of a synthetic vitamin E counteracts the dysfunction of both systems as well as their chief symptom, creatinuria, in that it effects fixation of creatine in the tissues.

J. A. M. A.

Neuropathology

DETECTION OF THE VIRUS OF POLIOMYELITIS. S. D. KRAMER, B. HOSKWITH and L. H. GROSSMAN, J. Exper. Med. **69:**49, 1939.

Five strains of the virus of poliomyelitis were recovered from nasal washings and feces. Four strains were of human origin; the fifth strain came from a monkey killed at the height of the disease. Of the human strains, the first was isolated from the feces of a 14 year old child seven days after the onset of illness. The second strain was from the nasal washings of a 6½ year old child five days

after the onset of illness. The single monkey strain was isolated from the upper intestinal segment, and this appears to be the only instance of isolation of a strain of this virus from such a source recorded in the literature. The authors state that the detection of the virus in the nasal washings of 2 additional patients who were convalescent lends further support to the belief that the virus of poliomyelitis is spread by human contact. Furthermore, the recovery of the virus from the gastrointestinal tract with as great or greater frequency than from the upper respiratory tract need not, it appears to these authors, alter the present concept of the mode of entrance of the virus into the body, namely, by way of the upper respiratory tract. If the presence of the virus in the upper respiratory tract is conceded, the passage of nasal and oral secretions into the gastrointestinal tract by reflex swallowing would serve to explain the presence of the virus in this tract. It might be further predicated that since the gastrointestinal tract functions as a temporary reservoir for secretions from the upper respiratory tract, the intestine should, after a time, contain the virus in higher concentration than any single sample of secretion obtained from the upper respiratory tract by nasal washing. Failures to detect the virus in the gastrointestinal tract are perhaps more indicative of the inadequacy of the procedures for the detection of the virus than of the absence of the virus. The recovery of the virus from the feces seven and nine days after the onset of illness takes on added significance. It indicates first that the virus withstands the gastrict acidity which under normal physiologic conditions tends to keep gastric contents relatively free from bacteria. It further suggests that improper disposal of feces from patients with poliomyelitis may have serious consequences for public health, particularly in smaller communities, where the inadequate disposal of sewage may result in contamination of surrounding beaches, or even local water systems. FROM AUTHORS' SUMMARY. [ARCH. PATH.]

PECULIAR ANATOMOCLINICAL FORM OF CHRONIC ALCOHOLISM: ALCOHOLIC LAMINAR CORTICAL SCLEROSIS. F. MOREL, Rev. neurol. **71**:280 (March) 1939.

Morel says that the neuroglia architecture may undergo profound transformations. For a number of years he has made systematic studies of the macroglia of the brains of patients with oligophrenia, dementia praecox, epilepsy, dementia paralytica, alcoholism, cerebral arteriosclerosis and, finally, senile degeneration. In all, he studied more than 400 brains. In this report he describes observations on 4 patients with chronic alcoholism. At the time of death their ages were 37, 51, 52 and 58 years, respectively. All had been greatly addicted to alcohol and presented signs of grave alcoholic gastritis. In their last years all had signs of alcoholic impregnation with prolonged atypical delirium tremens. Spasticity of the legs rendered walking difficult; there were severe tremor of the hands, with mild carphology, quivering of the face and stuttering. The Wassermann reaction of the blood as well as of the cerebrospinal fluid was negative in all 4 patients. Examination of the brains revealed that their weights were relatively high. There was subarachnoid edema, but no fibrous leptomeningitis typical of dementia paralytica and no granular ependymitis. On the other hand, there was considerable cerebral arteriosclerosis. On microscopic examination, none of the 4 brains presented senile plaques or cellular changes of the Alzheimer type. There were no changes characteristic of dementia paralytica. All 4 brains presented proliferations of the neuroglia. These proliferations were not neuroglia islands or discontinued nests, which in places may have a laminar aspect but which in fact are pseudolaminar; on the contrary, they formed a continuous stratum limited to the third layer. Symmetric regions of the brain always showed a remarkable similarity with respect to the extension and the intensity of this proliferation. It was especially pronounced in the frontal lobe, but in the ascending frontal convolution it was not as noticeable as in the other frontal convolutions. It was again more pronounced in the parietal region, but toward the occipital lobe it tended to disappear. As regards the condition of the neuroglia in the third layer, the author says that the astrocytes in the third layer had numerous thickened vascular pedicles

and that they were stretched out. Thus, it may be said that there were hyperplasia, hypertrophy and alteration of the astrocytes in the third layer. The microglia of the third layer likewise had undergone changes. Although in other parts of the cortex it was relatively fine and delicate, in the third layer it was coarse. The alterations presented by the nerve cells of the third layer were not particularly characteristic. The author suggests for the cerebral modification described the term "alcoholic laminar cortical sclerosis." J. A. M. A.

Psychiatry and Psychopathology

PSYCHOSES WITH PERNICIOUS ANEMIA. G. A. WILTRAKIS and A. V. PARTIPILO, Illinois M. J. **76**:562 (Dec.) 1939.

From 1931 to 1938, Wiltrakis and Partipilo encountered 24 cases of pernicious anemia among the 13,023 patients with mental disease admitted to the Elgin State Hospital. In addition to the anemia, the diagnosis in 9 cases was psychosis, in 7 paranoid symptom complexes, in 3 psychosis with cerebral arteriosclerosis and in the others various mental conditions. Pernicious anemia was considered the primary cause of the psychosis in 16 of the 24 cases. In 12 the anemia was observed prior to the onset of mental symptoms, and in the remaining 4, within a maximal period of one year after the onset of psychosis. The psychosis of pernicious anemia is not characterized by any specific form of mental behavior; yet certain mental symptoms predominate. Marked irritability is frequently present, and paranoid states, confused states and depressions are observed often. Undoubtedly the prepsychotic personality is of considerable importance in the reaction pattern. Prominent among these symptoms are marked irritability and uncooperativeness. The adjectives frequently used in the literature in describing the behavior of these patients are irritable, stubborn, peevish, surly, obstinate, disagreeable, faultfinding, cantankerous and refractory. A pronounced symptom in 9 of the 16 cases was irritability. Prognosis in this psychosis is poor; yet mental recoveries occur, and the patients should be given the benefit of prolonged and extensive antianemia therapy. J. A. M. A.

TRANSFERENCE PROBLEMS IN SCHIZOPHRENICS. FREIDA FROMM REICHMANN, Psychoanalyt. Quart. **8**:412, 1939.

Schizophrenic persons are those who have suffered severe trauma in infancy, before the ego and the ability to examine reality have been developed, i. e., at a time when the infant lives grandiosely in a narcissistic world and expresses its needs and desires by gestures and movements. The trauma is a blow to the infant's egocentricity, and because it occurs during the period of greatest security it makes him extremely oversensitive to frustration. Slight frustration may be beyond the limit of the child's endurance, and he escapes unbearable reality by reestablishing the autistic delusional world of infancy.

When psychoanalytic treatment is initiated, he is suspicious and distrustful of the analyst, because he feels that the latter will compel him to return to the frustrations of real life, and that this will reveal his inadequacy and will subject him to a repetition of the aggressive interferences which met his initial symptoms and peculiarities. Although he longs for human contact, he is afraid to admit this longing to himself or to the analyst for months or years, lest he experience frustration. When he does accept the analyst he becomes greatly dependent, and slight frustrations arouse as much anxiety as would the withdrawal of supporting forces in infancy. The patient reacts to the anxiety by increasing hostility or withdrawal. Strong transference reactions are developed by schizophrenic patients and are often not understood by the analyst. The analyst and the patient live in different worlds and at different levels of development. The patient often interprets the analyst's involuntary reactions as he interprets his own, and if he accepts the analyst he expects the latter to carry out all his wishes. The analyst often mis-

understands the patient, and if he cannot accept the fact that a misunderstanding has occurred the patient may lose confidence, feel insecure and respond by outbursts of rage. These outbursts of rage are accompanied by anxiety, feelings of guilt and fear of retaliation, which lead to more hostility, and a vicious circle quickly appears. The schizophrenic person is capable of developing strong feelings of love and hate.

Therapy must be modified, as follows: Analysis should be preceded by a long preparatory series of daily interviews to establish contact, as is done in child analysis. There should be no request to lie down or attempt to force the patient to give free associations. The analyst should not ask questions if he does not understand the material; neither should he give interpretations to prove he knows what the patient is talking about, for the patient understands his own unconscious better than the analyst. It is not intellectual comprehension that helps the schizophrenic person, but the sympathetic understanding and skilful handling of the patient's and the physician's mutual relationship. PEARSON, Philadelphia.

DEVELOPMENTS IN THE PSYCHOANALYTIC CONCEPTION AND TREATMENT OF THE NEUROSES. SANDOR RADO, Psychoanalyt. Quart. **8**:427, 1939.

The capriciousness of the practical results of psychoanalytic therapy indicates that there was something missing in Freud's original formulation of the neuroses which stated that, because of repression of instinctual urges in childhood, it was the task of psychoanalysis to remove the resistances and allow this repressed pathogenic material to become conscious. Although this formulation has remained the keystone of psychoanalytic therapy, Freud later decided that it was anxiety which causes the repression and that the repression results in a neurosis.

Rado accepts the idea that the neuroses are caused by anxiety, but believes that they are a disturbance of the integrative function of the ego. He contrasts fear and anxiety and points out that fear, anxiety and pain are emergency devices by which the ego may produce emergency control measures in a situation which would cause danger and suffering to the subject. He believes that anxiety is a reflex response, developed earliest in childhood as a result of sense perceptions of real impending danger, and that it prompts the ego to reactive emergency measures. Later, as intelligence develops, the anxiety reflex is transformed into a fear reflex, and the motor manifestations of anxiety are replaced by the intellectual content of fear. With the evolution of fear, anxiety withers away. If development proceeds abnormally, the fear response develops but the anxiety reflex remains. The latter is not useful because it paralyzes ego action instead of calling forth a reactive adjustment. At first, anxiety attacks occur in situations in which the child normally would experience fear; later, they occur independently of such situations. The ego dreads the recurrence of such attacks and acquires morbid fears and faulty measures which upset its function to avoid the fears. The ego is unconscious of the meaning and source of the neurotic manifestations, because these manifestations are intimidating and humiliating. The emergency measures which upset ego function are disturbances of genital function, disturbances of the group and competitive functions and self injuries. Treatment must place emphasis on the damage inflicted by anxiety to normal functions rather than on the secondary consequences of the disturbance. PEARSON, Philadelphia.

ACUTE PSYCHOSES FOLLOWING SURGICAL PROCEDURES. HUGH H. MILLER, Brit. M. J. **1**:558 (March 18) 1939.

Miller discusses the fact that mentally normal persons occasionally become psychotic after surgical operations. This illness is an acute confusional psychosis, due to a toxic state. An infected wound is usually the source of the toxin. The prospects of rapid recovery from the acute symptoms are good, given efficient and early drainage. The occurrence of residual symptoms is related to the duration

and extent of septic absorption before the psychosis. Only rarely are residual symptoms so marked as to require persistent treatment in a hospital for mental disease.

ECHOLS, New Orleans.

SCHIZOPHRENIC THINKING IN A PROBLEM-SOLVING SITUATION. NORMAN CAMERON, J. Ment. Sc. **85**:1012 (Sept.) 1939.

Cameron takes issue with authorities who find a similarity between schizophrenic thinking and the thinking of children and old people. He points out that there is too much uncritical use of the words "regression" and "deterioration" in connection with schizophrenia. To clarify further the essentials of schizophrenic thought disorder, the author used the Hanfmann-Kasanin blocks, which he finds a particularly suitable medium for the investigation of thought processes. The principle of this method lies in the ability of the subject to form new concepts. The author's qualitative analysis of the thinking of severely disorganized schizophrenic patients indicates that the most striking characteristic is the overinclusion of environmental and imaginal material in the neutral problem itself. The patients could not eliminate from the function pattern those elements which the normal adult would treat neither as belonging to the same plane as the problem nor as amenable to the same operations. This incapacity may be observed not only by the experimenter but by the patient as well. A comparison is made of the psychologic boundaries as they appear in the thought of schizophrenic persons, of normal adults under special circumstances and of oligophrenic persons, as described by Lewin.

The schizophrenic patients called for changes in the rules of procedure and in the materials, and declared the situation rather than themselves to be inadequate. This phenomenon resembles their reactions to the inflexible order of real events in their own life situations. There was frequent noncorrespondence between what the patient actually did and what he said he had done, and between the perceptual pattern and the patient's formulation of it. A simple color grouping, for instance, was characterized in some other way, often more complex, and quite at variance with the patient's operation or its result. Act, or pattern, and word seemed often to belong to different systems of integration. Generalizations were numerous, and shifts from one hypothesis to another occurred without evidence of unusual difficulty. The generalizations were unsuccessful because they were too broad, too involved or too entangled with personal problems and fantasies, or because the language structure was so disorganized that it could neither function as social communication nor serve as a basis for the patient's own performance. Moreover, the generalizations, even when correct, often did not lead to any corresponding act.

KASANIN, San Francisco.

MATERNAL AGE, ORDER OF BIRTH AND DEVELOPMENTAL ABNORMALITIES. L. S. PENROSE, J. Ment. Sc. **85**:1141 (Nov.) 1939.

Penrose found that in a group of 224 mongolian idiot children the mean maternal age was 37.4. In his series of 1,132 cases of mental defect other than mongolism the mean age of the mothers was 29.4. The probability that a mother will have a mongolian idiot child is more than doubled for every increase of 5 years after the age of 25. The same applies to anencephaly, hydrocephaly and spina bifida. In 441 cases of these congenital defects and malformations the mean maternal age was 31.7. Maternal age is also an important factor in placenta praevia centralis. Congenital pyloric stenosis is more apt to occur in the first born.

KASANIN, San Francisco.

FEEDING IN INFANCY AND SUBSEQUENT PSYCHOLOGICAL DIFFICULTIES. B. C. F. ROGERSON and C. H. ROGERSON, J. Ment. Sc. **85**:1163 (Nov.) 1939.

The purpose of this investigation was to study the relation, if any, which exists between feeding difficulties experienced in infancy and the subsequent development

of the child when he has attained school age, as measured by his achievement, behavior and psychologic status. The group of children studied did not belong to a psychiatric clinic, and it was hoped that the analysis of such a group would, in addition, throw light on the occurrence and relative frequency of psychologic difficulties in the period of childhood of a presumably normal section of the population. Children who were entirely breast fed during infancy were regarded as the group without feeding difficulties; children who received more or less artificial feeding in infancy, as the group with feeding difficulties. The term "infancy" has been used throughout to denote the period from birth to the introduction of solid foods into the diet.

The breast-fed group consisted of 62, and the artificially fed group of 47 children. The total number of children included in the study was 223, but only in 109 cases was it possible to have the intensive follow-up observation from infancy to the age of 7. The authors believe that the fact that a child had to be artificially fed is an indication of a feeding difficulty. In comparing the two groups the authors found that breast-fed infants showed marked superiority over artificially fed infants. Comparison of the two groups showed a higher percentage of sickly infants in the artificially fed group. The mothers of the children were carefully questioned as to he presence of various neurotic traits, such as sleep disturbances, enuresis, jealousy of younger children, fears, "nervousness" and terrifying dreams. The authors find a definite association between feeding difficulties in infancy and subsequent psychologic maladjustment of the child at home and at school.

KASANIN, San Francisco.

THE PROGNOSIS IN SCHIZOPHRENIA BASED ON A FOLLOW-UP STUDY OF 129 CASES TREATED BY ORDINARY METHODS. HARRY STALKER, J. Ment. Sc. **85**:1224 (Nov.) 1939.

This investigation is a follow-up study of all the first patients admitted for schizophrenia to the Royal Edinburgh Hospital for Mental and Nervous Disorders during the five year period from Aug. 1, 1932, to July 31, 1937. None of the patients had received special treatment, such as convulsion therapy. The follow-up study was begun in September 1938. Of 133 patients 129 were traced. Fifteen (12 per cent) had complete remission; 11 (8 per cent) a social remission; 12 (9 per cent) were at home, improved; 27 (21 per cent) had a remission followed by a relapse, and 64 (50 per cent) were not improved. All the usual features, both in the patient's previous life and in his illness, which were regarded as having prognostic significance were estimated in each case and correlated with the results of the follow-up study. It was found that the following features were of favorable prognostic import: (1) healthy habits of reaction in the patient's previous life; (2) preponderance of environmental and psychogenic causes of the illness over the constitutional factors; (3) acute and recent onset of the illness; (4) well retained affective responses in the illness, with absence of disharmony between the affect and the thought content (manic-depressive symptoms were favorable), and (5) an acute type of schizophrenic illness, which could not be fitted into any of the four standard subgroups.

It was found that the following features had no prognostic import: (1) a family history of mental disorder; (2) the sex; (3) the educational attainment; (4) the age at onset of the illness; (5) tuberculosis, whether in the patient or in his family; (6) focal sepsis; (7) regressive symptoms; (8) hallucinations; (9) symptoms reflecting the cause. A number of other features were investigated, but no conclusions could be drawn, as the number of instances in which they occurred was too low to be considered.

The case records of the 15 patients with complete remissions were analyzed from the point of view of the general reaction, and the following classification was made: *Group 1.*—One patient with a psychopathic state who had an intercurrent paranoid-schizophrenic episode. *Group 2.*—Patients with schizoid personalities having schizophrenic episodes. Subgroup A: Seven patients all of whom had

passed through a long phase of subjective conflict and maladjustment. The cases in this subgroup all correspond closely to those which Kasanin described in his series of acute schizoaffective psychoses. After a short illness the patients recovered, and several became better adjusted than they had even been before. Subgroup B: Four patients with schizoid personality, well adapted in a sheltered environment, who broke down after minor stresses and then made a quick recovery to their usual level. *Group 3.*—Two patients in whom anxiety symptoms were prominent at the onset. *Group 4.*—One patient whose records were insufficient for full analysis of the reaction.

KASANIN, San Francisco.

CLINICAL CONTRIBUTION TO METRAZOL TREATMENT OF MENTAL DISEASES. V. MARTINENGO, Arch. f. Psychiat. **100**:123 (June) 1939.

Martinengo treated with metrazol about 200 patients, 150 of whom had schizophrenia and the others chiefly manic-depressive psychoses, with the following results: Over 75 per cent of patients with schizophrenia of less than eighteen months' duration had complete remissions; practically all the others showed some improvement. Patients with chronic disease, of over eighteen months' duration, showed the reverse tendency—in 66 per cent there was no effect at all and in only 5 per cent was there a complete remission. The best results were obtained in patients with manic-depressive psychoses, mostly evidenced as shortening of the duration of the attack. These experiences led the author to conclude that in physically healthy persons there is no danger of complications, and that only severe physical diseases, such as cardiovascular or pulmonary disorders, can be considered as definite contraindications. Hence, he urges the abolition of the rule requiring the permission of relatives for such treatment. The therapeutic effects of this method of treatment, the ease with which it is administered and the lack of dangerous complications render this method preferable to any of the others recently introduced. In fact, the author suggests that this method has been successful in cases in which other methods, such as insulin shock, fever therapy and leukotomy, have proved unsuccessful.

MALAMUD, Worcester, Mass.

Diseases of the Brain

NEUROSURGICAL TREATMENT IN CASES OF SYPHILIS INVOLVING THE OPTIC NERVES. E. HARTMANN, M. DAVID and L. GUILLAUMAT, Ann. d'ocul. **175**: 877 (Dec.) 1938.

Hartmann, David and Guillaumat report 4 cases of syphilitic lesions resulting in papilledema or atrophy of the optic nerve in which benefit was obtained through surgical intervention. In the first case the patient presented progressive intracranial hypertension, violent and persistent headaches, dizzy spells, attacks of blurred vision and papilledema, which were diagnosed as due to cerebral tumor. There was no clinical evidence of syphilis. The Wassermann reaction of the spinal fluid was negative. Surgical intervention revealed a gumma which histologically resembled a syphilitic granuloma. The Wassermann and Kahn reactions of the blood were strongly positive. Papilledema disappeared after removal of the gumma. In the second case surgical intervention revealed ventricular distention caused by syphilitic arachnoiditis of the cisterna magna, with stenosis of the lower orifice of the fourth ventricle. In the third case ventriculographic examination, by ruling out a tumor, permitted the tentative diagnosis of encephalitis and cerebral edema in a case of syphilis in the second stage. Decompression was effective after antisyphilitic treatment failed. The fourth case was one of arachnoiditis and vascular compression of the chiasm associated with tabes. Surgical intervention revealed the presence of optochiasmatic arachnoiditis.

BERENS, New York.

FATAL TRAUMATIC DISORDERS OF THE BRAIN, ESPECIALLY BERNER'S HEMORRHAGES IN THE MEDULLA OBLONGATA, AND THEIR MEDICOLEGAL SIGNIFICANCE. F. HARBITZ, Nord. med. **4**:3441 (Nov. 25) 1939.

Harbitz discusses the anatomic manifestations in 165 cases of cerebral disorders of traumatic origin, including 62 in which he himself performed necropsies. Epidural and extradural hemorrhages occurred in 27 cases, with simultaneous hemorrhages in the interior of the brain in only 4. Subdural hemorrhages were observed in 93 cases and were massive in 19; intermeningeal or subarachnoid hemorrhages occurred in 112 cases, often with subdural and cortical hemorrhages. Cortical hemorrhages were seen in most of the cases. "Central" hemorrhages were established in the central ganglia in 18 of the author's personal cases, and simultaneously or independently in the pons Varolii or around the aqueduct of Sylvius in 16—in all in about one third of his cases. These hemorrhages were regularly found in connection with fracture of the skull and bleeding in the membranes of the brain and in the cortex; they were usually inconsiderable, were perivascular and subependymal and in most cases were demonstrable only microscopically. Hemorrhages in the medulla oblongata appeared in 23 of the author's personal cases, or in about 37 per cent. They were often absent in cases in which there were small lesions of the head, especially when there were simultaneous lesions of the chest and abdomen with internal hemorrhage. Usually they were demonstrable only microscopically and were perivascular, without destruction of nerve tissue, with simultaneous perivascular hemorrhages in other central parts of the brain. There were regularly other marked intracranial changes: large skull fractures; hemorrhages, often considerable, in the membranes of the brain, and, especially, large cortical hemorrhages and now and then general edema of the brain. The author assigns little medicolegal significance to the inconstant perivascular hemorrhages and asserts that similar hemorrhages have been established in the medulla oblongata in cases of sudden nontraumatic death and have been absent in cases of fatal trauma of the head with symptoms of concussion. He does not regard the base of the fourth ventricle as a site of predilection for such hemorrhages and did not in any of the 165 cases find an isolated massive hemorrhage in the medulla oblongata which could be considered as certainly or probably of traumatic origin and the cause of death. Five so-called nearly pure cases of concussion of the brain are described, in which, mainly by microscopy, small hemorrhages were established in various parts of the brain, not usually in the medulla oblongata. In his opinion no definite anatomic changes can be regarded as the essential and certain cause of the symptoms of concussion of the brain. He stresses that edema of the brain, when present, is an expression of general circulatory disturbance of great importance in explaining the phenomena and eventually the cause of death. He doubts whether fatal traumatic disturbances of the brain occur without anatomic changes and maintains that on the whole from the anatomic point of view there is no sharp division between contusion of the brain and concussion.

J. A. M. A.

Diseases of the Spinal Cord

FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS. H. CURSCHMANN, Deutsche Ztschr. f. Nervenh. **149**:133 (Aug. 1) 1939.

Curschmann reports the history of a woman aged 74 who stated that as a young girl she had had paresis and muscular dystrophy in the forearms. The increase in the muscular atrophies was extremely slow, so that until six years before he saw her the patient was able to work with her hands. Impairment of the ability to walk dated back only a few years. Severe degenerative muscular atrophy was noticeable particularly in the radial region, but the other muscles of the hand and arm also were involved. Electrical irritability of the atrophic muscles was practically abolished. The muscles of the shoulder and pelvic

regions were unimpaired. The patient died of cardiac insufficiency, pyelocystitis and pneumonia. Microscopic examination of the spinal cord corroborated the diagnosis of progressive spinal muscular atrophy, although the expected degenerative changes in the lateral and anterior pyramidal tracts were not observed. This is surprising, since some of the symptoms indicated involvement of these tracts. Especially noteworthy are the early onset, the slow progress, the comparatively mild course, the predominant involvement of the radial region and the absence of bulbar paralysis. However, of primary interest is the fact that a brother of the patient presented during his youth the same form of muscular atrophy in the arms and legs. The author is convinced that this is an example of progressive amyotrophic lateral sclerosis in 2 siblings. A review of the literature, especially that of recent years, revealed that the familial occurrence of amyotrophic lateral sclerosis is not as rare as was formerly believed. Among others, he cites Kalinowsky, who observed a woman with amyotrophic lateral sclerosis, whose 2 daughters had a bulbar paralytic syndrome with atrophy of the small manual muscles; Kreyenberg, who detected amyotrophic lateral sclerosis in 3 siblings; Montanaro and Lopez, who observed amyotrophic lateral sclerosis in a father and 3 sons, and several other authors who made similar observations. He thinks that in the future careful neurologic studies should be made on the members of the families of patients with spinal amyotrophy and with amyotrophic lateral sclerosis and that studies on twins should also give attention to this group of disorders.

J. A. M. A.

RELATION BETWEEN THE NERVOUS SYSTEM AND THE CIRCULATION, BASED ON OBSERVATIONS DURING OPERATIONS ON MAN. O. FOERSTER, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:439 (Aug.) 1939.

The vascular reaction to heat and cold and to mechanical, chemical and electrical stimuli persists in an upper extremity in which the whole brachial plexus is cut. The pallor in response to cold and the erythema resulting from warm stimuli persist longer in the denervated extremity than in the other limb. Reflex responses are absent in the denervated limb when distant parts are stimulated. Persistence of these local reactions is probably due to the fact that sympathetic fibers pass directly to the subclavian and iliac arteries. Totally deefferented striated muscle responds to stimuli applied to the muscle itself and to parasympatheticomimetic substances injected into the blood stream. Foerster mentions the case of a boy aged 11 years in whom the median and ulnar nerves were completely severed after a bite from a dog. He was able to produce strong flexion of the fingers by injecting 1 cc. of choline (probably acetylcholine) into the brachial artery. The flexion of the fingers gradually relaxed after the injection of epinephrine. The smooth muscle of the blood vessel wall seems even more sensitive to chemical influences after the nerve supply to a given part is cut. Marked vasodilatation in the distribution of a cut nerve can be produced by pilocarpine injected subcutaneously.

Only vasodilatation can be produced by direct electrical stimulation of a peripheral nerve. Undoubtedly, sympathetic vasoconstrictor fibers are present in the nerves, though there is no known method delicate enough to stimulate them during their course in the peripheral nerve. Vasoconstriction in the human being can be readily produced by stimulating the sympathetic ganglia or fibers. Marked hyperemia usually follows sympathectomy. The mucous membranes of the nose on the side of operation sometimes become so swollen and hyperemic that the sense of smell is lost.

White and his associates have emphasized the advantage of preganglionic ganglionectomy in the treatment of angiospastic conditions in the upper limbs. The better results of sympathectomies in the lower limbs have probably been due to the fact that they have been preganglionectomies. Foerster reports a brilliant result in a case of Raynaud's disease in which he performed preganglionic section of the second and third thoracic roots. When preganglionic sympathectomy is

done one does not see the increased sensitivity of the blood vessels to epinephrine or to local stimulation with cold. Foerster mentions a case in which he extirpated the stellate ganglion and the patient suffered severely (with gangrene) when he exposed the sympathectomized limb to cold. The preganglionic section is, in addition, a simpler operative procedure.

Stimulation of the first and second anterior thoracic roots causes vasoconstriction of the neck and face, and that of the third, fourth, fifth and sixth anterior thoracic roots, vasoconstriction in the upper extremity. This can be demonstrated well by means of the plethysmograph. There is still doubt whether the seventh thoracic nerve has vasoconstrictor fibers. Section of the sympathetic strand between the second and the third thoracic nerve cuts all preganglionic vasoconstrictor fibers to the upper limb. Foerster's stimulation experiments on man show that vasoconstrictor fibers to the lower limbs pass through anterior roots of the tenth, eleventh and twelfth thoracic and the first and second lumbar nerves. Section of the sympathetic strand between the second and the third lumbar nerve removed most of the preganglionic fibers to the lower limbs.

Segmental vasodilatation of the skin was produced by electrical stimulation of the distal ends of the cut dorsal roots throughout the length of the cord. This is due to stimulation of efferent vasodilator fibers which pass through the posterior roots. The existence of such fibers is corroborated by the demonstration of intact nerve fibers in the posterior roots four years after posterior rhizotomy.

Operations to lower arterial hypertension by cutting the sympathetic strands in the abdomen may also have a beneficial effect by cutting off the nerve supply to the adrenal glands. The possibility of an operative approach to this problem by hypophysectomy is suggested, since the basophilic elements are said to secrete a hormone which raises the blood pressure.

Section of the cord in the lower cervical or upper dorsal segments in man is often followed by dilatation of the vessels of the skin below the level of the lesion with increase in the temperature of the skin. The blood pressure also drops in some cases. This vasodilatation is probably due to section of the descending pathways from a suprasegmental diencephalic vasoconstrictor center. After about 100 chordotomies, Foerster noted a drop in blood pressure in a significant number of cases. In 1 case it fell from 270 to 100 mm. of mercury, and later did not exceed 140 mm. To obtain such changes in blood pressure the most dorsal part of the spinothalamic tracts must be cut. The problem of chordotomy as a means of lowering blood pressure merits further investigation. Total section of the cord in the middorsal region causes the disappearance of the vasoconstrictor reflex from one lower limb to another or from the upper to the lower limbs. The reflex from one upper to the other upper limb remains intact. The vasodilator reflex is intact below the level of section of the cord. SAVITSKY, New York.

Peripheral and Cranial Nerves

PAINFUL HEMISACRALIZATION. F. STEFANI, Chir. d. org. di movimento **24**:565 (Aug.) 1939.

According to Stefani, pain in cases of hemisacralization of the fifth lumbar vertebra is due to irritation of osteoperiosteal sensory nerve fibers, without any neural or radicular lesion. The sensory and motor innervation of the leg, lateral to the area of pain, is normal in cases of hemisacralization, whereas it is disturbed in cases of pain of neuritic or radicular origin. The coexistence of roentgenographic abnormalities of the vertebra and normal sensory and motor innervation of the leg indicates hemisacralization. The author proposes a procedure for testing the normality of innervation of the lateral part of the leg. It consists of the injection of a small dose (not specified by the author) of an anesthetic in solution over the apex of the macroapophysis, the presence of which is previously determined by roentgen examination of the sacrolumbar segment. The injection is made under roentgenoscopic control, with a needle of about 8 or 10 cm. Diffusion

of the anesthetic to nearby structures is avoided. Pain from hemisacralization disappears immediately after the injection. The leg regains function. Both pain and dysfunction of the leg return as soon as the effect of the anesthetic is over. Neither sensory nor motor disturbances appear in the leg in the course of or after the test (positive results from the procedure). Pain from sacralization complicated by either neuritis or radiculitis disappears after the anesthetic from the lumbosacral region and the upper part of the leg, whereas it is not modified at the lower part of the leg (partial positive results from the procedure). Lumbosacral pain of either neuritic or radicular origin either is not modified or is slightly modified simultaneously with appearance of sensory and motor disturbances of the leg. According to the author, the procedure is of value for the diagnosis of painful sacralization and also for deciding on the operation, which is resection of the macroapophysis. Five cases are reported. Two patients recovered from the operation (resection of the macroapophysis). There was 1 case of the mixed form and 1 each of rheumatic and spondylosthesic lumbosacral pain.

J. A. M. A.

ROLE OF RADICULAR NERVES IN HUMAN TETANUS. L. BENEDEK and A. JUBA, Confinia neurol. **2**:345, 1939.

Benedek and Juba, in an earlier report, described the histopathologic aspects in 10 cases of tetanus. In this paper they give an account of studies in 4 additional cases. The presence of a contusion or wound provided the prerequisite for the invasion of the anaerobic tetanus bacillus, and symptoms like lockjaw, stiffness of the neck and rigidity of the muscles were so pronounced in all 4 cases that the diagnosis could not be doubted. The histopathologic aspects in the first 2 cases were especially varied; in the third case they were absent, and in the fourth case they were uncommonly extensive. In the first 2 cases the infiltrations of the radicular nerves, consisting chiefly of lymphocytes and leukocytes, were so considerable that in some places the connective tissue framework was completely filled with them. The radicular nerves presented the most serious changes, although in case 1 there existed extensive, and in case 2 localized, infiltration of the pia mater. There seems to exist a correlation between the duration of the disease and the histologic picture. In case 1 the disease lasted four days. The infiltrations, located in the radicular nerves and in the pia mater, were grave. In case 2 in which the disease lasted eight days, the infiltrations were less extensive, existing chiefly in the radicular nerves. In case 3, in which the disease had lasted ten days, no histologic changes were observable. All this confirms the opinion which the authors had expressed previously, that the gravity of the infiltration depends chiefly on the duration of the disease. Case 4, however, apparently is a contradiction, for in spite of the long duration (seventeen days) of the disease there remained sparse infiltrations in the fibrous sheaths of the radicular nerves and severe infiltrations in the pia mater. In all probability the infection in this case was particularly virulent. In this new series of cases, as in the earlier one, the lesions of the cells of the intervertebral ganglia were more severe than those of the motor elements of the spinal cord. The swelling of the axis-cylinders of the radicular nerves was also common, while the myelin sheaths were unimpaired. The authors think that the infiltrations in the nervous system, particularly those in the connective tissue of the radicular nerves, are a manifestation of the increased activity of the reticuloendothelial apparatus of the central nervous system.

J. A. M. A.

Vegetative and Endocrine Systems

ACUTE ABDOMINAL SYNDROMES OF HYPOPHYSIAL ORIGIN. G. MARAÑÓN, C. RICHET, A. PERGOLA and G. LESUEUR, Lisboa méd. **16**:589 (Oct.) 1939.

Marañón and his collaborators call attention to the frequency of acute abdominal syndromes in patients suffering from hypophysial insufficiency. Seven cases are

reported. In all cases the insufficiency was shown by the presence of any or several of the following conditions: diabetes insipidus, dyschromia, sexual disorders, increased temperature, progressive thinness, cachexia (or adiposity) and obstinate constipation. The authors found that acute abdominal syndromes of hypophysial origin can be divided, according to their type, into two large groups: those with predominant intestinal paralysis (which simulate ileus paralyticus) and those with predominance of spasm and pain (which simulate acute appendicitis, perforated peptic ulcer, cholecystitis or some other acute abdominal condition). The abdominal symptoms of either the paralytic or the acute abdominal type are controlled in all cases by administration of extracts of the posterior lobe of the hypophysis. Discontinuation of the treatment frequently results in reappearance of the symptoms. The authors believe that the abdominal symptoms of the paralytic type are due to absence (or diminution) of the hormone of the posterior lobe of the hypophysis with consequent development of intestinal paralysis, whereas those of the type of acute abdominal conditions are due to absence (or diminution) of either the parathyrotropic or the adrenotropic hormone with consequent parathyroid or adrenal insufficiency. The authors point out the importance of a differential diagnosis between the acute abdominal syndrome of hypophysial and that of nonhypophysial origin, especially because the lack of a proper diagnosis may lead to useless surgical intervention in the case of patients who are suffering from abdominal syndromes of hypophysial origin.

J. A. M. A.

TRANSITORY FRÖHLICH'S SYNDROME ON A CONSTITUTIONAL BASIS. W. DZIERZYNSKI, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:81 (March) 1939.

Dzierzynski reports 5 cases of adiposogenital dystrophy in boys between 10 and 14 years of age. All showed definite improvement as they were observed for a few years. The syndrome was apparently benign and transitory. No roentgenographic or other evidence of organic disease of the perichiasmal or hypothalamic region was found. There was also no indication of chronic encephalitis. All the patients' mothers were obese and showed a tendency to hyperglycemia. All but 1 had hypercholesteremia. The author considers this syndrome a distinct clinical variant of Fröhlich's disease, probably with a constitutional genetic basis.

SAVITSKY, New York.

Treatment, Neurosurgery

EVALUATION OF VITAMIN B_1 (THIAMIN CHLORIDE) IN THE TREATMENT OF POLYNEURITIS. MARTIN G. VORHAUS, Am. J. M. Sc. **198**:837 (Dec.) 1939.

Vorhaus reports on a study of 520 patients with neuritis, of whom about 60 per cent were females and about 40 per cent males. Over 72 per cent of the patients were between the ages of 30 and 59. The average daily dose of thiamine hydrochloride for the entire series ranged from 3 to 10 mg., i. e., from about 1,000 to 3,000 international units daily. The average total duration of treatment was about nine weeks for the entire series. Approximately 80 per cent showed a maximum relief of symptoms in three months or less. Of 170 patients under observation up to one year after discontinuing thiamine, 21 per cent showed recurrences. Of 111 patients under observation from one to two years after discontinuing thiamine, 71 per cent showed recurrences. Of 95 patients under observation from two to three years after discontinuing thiamine, 85 per cent showed recurrences. Of 123 patients observed more than three years, 96 per cent showed recurrences. Readministration of thiamine in these recurrences was highly effective. For persons who may have a greater normal need for thiamine than can be obtained from a normal diet the term "primary hypothiaminosis" is suggested.

MICHAELS, Boston.

TREATMENT OF OTITIC MENINGITIS. D. S. CUNNING, Arch. Otolaryng. **30**:950 (Dec.) 1939.

According to Cunning, attempts at treatment of otitic meningitis have been disappointing. Reports covering several thousand cases indicate mortality rates of from 95 to 98 per cent. In this paper Cunning describes the treatment and results in 14 cases of otitic meningitis and in 1 case of meningitis following submucous resection. Only cases in which the pathogenic organism was actually recovered from the spinal fluid are included in this report. Treatment was similar in all cases, namely, a combination of radical surgical intervention, daily spinal drainage and the intensive use of sulfanilamide or one of the related compounds. Blood transfusions and intravenous administration of dextrose were employed during the same period. In this series of 15 consecutive cases of meningitis, 11 patients recovered and 4 died. Sulfanilamide, while obviously extremely important in treatment, is apparently not sufficient in itself to produce a cure. Surgical intervention in itself is not sufficient, and it seems that a combination of the two, namely, sulfanilamide and surgical intervention, offers the best hope. In the use of the drug it is important that treatment be started early, that the dose be large and that the treatment be continued for several weeks after cessation of symptoms. Surgical measures, likewise, should be instituted as soon as the diagnosis is made. In 7 of 8 cases in which the invading organism was Streptococcus haemolyticus, recovery occurred. In 2 cases in which the organism was pneumococcus type I and in 1 case in which the organism was pneumococcus type III, death occurred. Had sulfapyridine been known when the pneumococcic infections were treated, the results might have been better. Six patients showed paralysis of the external rectus muscle. It seems that with the use of sulfanilamide plus surgical intervention meningitis is not necessarily to be considered as formidable as formerly.

J. A. M. A.

GENOSCOPOLAMINE [SCOPOLAMINE HYDROBROMIDE]: ITS USE IN PARKINSONISM. JOHN H. SCHARF and STEPHANE T. MANONG, J. Nerv. & Ment. Dis. **89**: 682 (May) 1939.

Scharf and Manong gradually substituted scopolamine hydrobromide for scopolamine, atropine or stramonium in the treatment of 22 patients with long-standing parkinsonism. The dose of scopolamine hydrobromide usually given was 2 or 3 granules (1 or 1.5 mg.) three times a day. The results were uniformly encouraging in that rigidity, tremor, weakness, salivation and oculogyric crises were better controlled than by scopolamine. Polyuria was noted in some patients. The arteriosclerotic form of parkinsonism responded less readily than the encephalitic variety.

MACKAY, Chicago.

SURGICAL TREATMENT OF MENTAL DISORDERS. W. FREEMAN, M. Ann. District of Columbia **8**:345 (Dec.) 1939.

Freeman and his associate have modified the original Moniz surgical technic for the correction of mental abnormalities. Freeman finds that prefrontal lobotomy produces a certain change in the personality of the patient, characterized by reorientation in the direction of extroversion and reduction in introversion. It eliminates obsessive thinking; it reduces self consciousness, and it promotes satisfaction with self and the surroundings. Fear of the future is no longer present. After operation the patient behaves differently; his behavior seems to depend to some extent on his original makeup and to some extent on the amount of frontal lobe that is still in connection with the rest of the brain. The most satisfactory results of the operation are achieved in cases of obsessive, compulsive neuroses and in those of the involutional depressions with agitation. The results for chronic alcoholism have been negligible, and those for the schizophrenias are still under consideration. Prefrontal lobotomy seems to offer something of value in the relief of intractable neuroses and psychoses.

J. A. M. A.

DRUG THERAPY IN CASES OF INFANTILE CEREBRAL PALSY AND ALLIED DISORDERS, WITH SPECIAL REFERENCE TO HYOSCINE. I. C. NICHOLS and S. R. WARSON, New England J. Med. **221**:888 (Dec. 7) 1939.

In treating patients with infantile cerebral palsy, Nichols and Warson carried out a program of training including hydrotherapy, massage and active and passive exercise. In considering a pharmacologic approach, also, the hypothesis was advanced that treatment with a drug in the atropine group might reduce the hypertonus, influence the athetosis, speed up the process of training and eliminate the drooling. The drug of choice was scopolamine hydrobromide, which they administered in 6 cases, with minor interruptions, for two and a half years. The usual maintenance dose was $\frac{1}{200}$ grain (0.0003 Gm.) given twice daily by mouth. There was no change in the program of treatment other than the addition of the drug therapy. During the course of this study the scopolamine was discontinued, and the effects of three other drugs, phenobarbital, benzedrine sulfate and atropine, were tested over periods of two weeks. The authors found that with scopolamine therapy drooling was abolished in all cases, the athetosis was lessened, confidence was increased, relaxation was improved and progress in retraining was more rapid. One child learned to walk in three days. No general contraindications to scopolamine were established. In particular, there were no increasing tolerance, no annoying side effects and no untoward symptoms even when the drug was suddenly withdrawn after as long as nine months. The favorable response to scopolamine came early or not at all. Benzedrine sulfate, phenobarbital and atropine sulfate, which were investigated clinically in the same series, proved disappointing.

J. A. M. A.

VALUE OF DIPHENYL HYDANTOINATE (DILANTIN) IN PSYCHOSES WITH CONVULSIVE DISORDERS. N. D. BLACK, Psychiatric Quart. **13**:711 (Oct.) 1939.

Black used dilantin in treatment of 17 patients with psychoses and convulsions who had not reacted well to other forms of chemotherapy. Two patients had complete relief from seizures (for a minimum of six months), and 7 others had reduction in the number and severity of the fits. The remaining 8 patients either were not influenced by the drug or showed an increase in the number and severity of convulsions. Mental improvement was in direct relationship to the control or reduction of the number of seizures. Treatment of 1 patient had to be discontinued because of toxic symptoms and of 3 patients because of an increase in the number and severity of seizures. Ten are still receiving the drug. Three patients died. The author believes that the use of the drug should be restricted to patients who do not respond to less toxic forms of treatment.

J. A. M. A.

GENERAL PARALYSIS AND ITS TREATMENT BY INTRAVENOUS T. A. B. [TYPHOID-PARATYPHOID A AND B VACCINE] VACCINE. C. E. ROACHSMITH and E. S. STERN, J. Ment. Sc. **85**:558 (May) 1939.

Seventy-five patients with dementia paralytica were treated with typhoid-paratyphoid A and B vaccine. Eighteen patients recovered and returned to work. Eleven improved by remaining in the hospital, and 41 died. Most of the patients who failed to recover died. In comparatively few cases did the disease become chronic. On comparing the number of patients with this disease admitted thirty years ago with that at the present time, the authors conclude that dementia paralytica is undergoing a decline in virulence. Thus, they point out that in the decade from 1905 to 1915 the proportion of patients with dementia paralytica to the total number admitted was 17.1 per cent, whereas in the decade from 1929 to 1937 it was only 10 per cent.

KASANIN, San Francisco.

INSULIN PREMEDICATION IN CONVULSION THERAPY. D. E. SANDS, Lancet **2**:250 (July 29) 1939.

The resistiveness, panic and fear accompanying convulsion therapy have been eliminated by Sands with insulin premedication in 22 of 23 cases of schizophrenia.

The insulin premedication has enabled him to complete convulsant treatments in the 22 cases which would otherwise have had to be terminated prematurely because of resistance and apprehension. In the instance in which treatment was stopped it was done because of the excessive exacerbation of symptoms on recovery from each convulsion. The patient's condition deteriorated, and it was considered inadvisable to continue the treatment. The high proportion of "negative fits"—30 per cent—which these resistive patients had without insulin was reduced to 13 per cent with insulin. But 3 patients have been discharged, and 1 has since had a relapse. This is an inferior figure compared with most of the published statistics and those of Claybury, the rate of discharge being 42 per cent. This use of insulin, by greatly diminishing the unpleasantness of convulsion treatment to resistive schizophrenic patients, has facilitated their nursing and management. The object in insulin premedication is to give such a quantity as will induce the patient to cooperate with the injection of a convulsant drug. The dose may require pushing until drowsiness and languor supervene. On almost every occasion the induction of the fit has been sufficient to dispel any lethargy induced by the insulin. The patients are given sugared tea to drink as soon as the convulsion is over. In 2 cases, owing to the development of sensitivity to insulin, recovery was effected with giving a solution of dextrose through the nasal tube on one occasion and with intravenous administration of dextrose on two other occasions. As with metrazol therapy, the management of the premedication can be performed by the ordinary nursing staff of the hospital for mental disease without the usual special training generally necessary for insulin shock therapy. J. A. M. A.

TREATMENT OF MIGRAINE BY INTRAMUSCULAR INJECTIONS OF METRAZOL. A. LEROY, J. belge de neurol. et de psychiat. **39**:735 (Nov.) 1939.

Leroy reports 3 cases of migraine in which metrazol was successfully given intramuscularly in doses varying, preferably, between 0.25 and 0.3 Gm. in a 10 per cent solution. One of the patients, aged 63, had suffered from migraine for fifty years. His attacks occurred every ten days, with violent headaches, vomiting and insomnia. Sixteen injections of from 0.2 to 0.3 Gm. were given during a period of four months, followed by a single injection of 0.3 Gm. about two months afterward. At the end of a further period of four and one-half months it was stated that the migraine appeared only at monthly intervals in an attenuated form of light headache, sometimes accompanied by vomiting. The condition of another patient, aged 35, whose mother had an anamnesis of migraine, dated back only a few years. He was subject to monthly attacks, sometimes lasting two weeks, with the usual signs. A strict dietary regimen was unavailing. Four intramuscular injections of from 0.2 to 0.25 Gm. of metrazol were sufficient to cure the disease, correct constipation and normalize nutrition. The disease of the third patient, aged 42, also with anamnesis of migraine in the mother, had a background of neurasthenia, debility, tachycardia and marked anemia. Crises of migraine occurring once a week and increasing in violence set in, a year before treatment, with nausea and vomiting. The administration of fourteen injections, usually of from 0.2 to 0.25 Gm. of metrazol, progressively reduced the symptoms. Three months later the patient was feeling well and had had only one or two slight attacks. The author attributes the efficacy of metrazol in treatment of migraine to shock induced by the intramuscular administration of the drug, but invites further study. J. A. M. A.

INTRASPINAL INSUFFLATIONS OF AIR IN TREATMENT OF MENINGOCOCCIC CEREBROSPINAL MENINGITIS. G. MURANO, Riv. di neurol. **12**:336 (Oct.) 1939.

In a previous article (*Pediatria* **47**:105 [Feb.] 1939) Murano reported satisfactory results from the administration of intraspinal insufflations of sterile air (pneumoencephalus) in association with antimeningococcus serum in the treatment of meningococcic cerebrospinal meningitis. In the first group of 5 infants,

who were suffering from the acute or the subacute form of the disease, there were 4 recoveries. The only failure was due to the presence of complete ventricular blockage when the treatment started. The treatment consists in administration of intralumbar injections of sterile air in doses varying from 15 to 25 cc., immediately followed by an intralumbar injection of antimeningococcus serum in doses varying from 8 to 20 cc. and an intramuscular injection of the same serum in doses of from 15 to 20 cc. The treatment is repeated every other day until three or four treatments are given. In this article the author reports satisfactory results from the treatment of 7 infants suffering from the acute or the subacute form of the disease. All the patients recovered. The author carried on roentgen examinations of the brain and found that the insufflations of sterile air keep open the communications between the ventricles and also between the ventricles and the subarachnoid spaces, and may break up the blockage of the ventricles and stimulate better circulation of the cerebrospinal fluid and elimination of the purulent fluid. In collateral researches on patients with normal meninges and on those suffering from the disease the author found that the insufflations of sterile air increase the permeability of the barrier between the blood and the meninges in both groups of patients. The increased permeability results in the passage of either antibodies or drugs from the blood to the cerebrospinal fluid in the course of the treatment with either meningococcic serum or certain drugs, such as sulfanilamide, which is valuable in the treatment of the condition. Administration of intraspinal insufflations of air is a harmless and well tolerated procedure. Neither early nor late complications were observed in the groups of patients observed by the author. They recovered without sequels.

J. A. M. A.

Muscular System

RELATION OF MYASTHENIA GRAVIS TO HYPERTHYROIDISM. MELVIN W. THORNER, Arch. Int. Med. **64**:330 (Aug.) 1939.

Thorner reports a case of myasthenia gravis in which hyperthyroidism later developed. The myasthenic symptoms were well controlled by prostigmine. In six months it was noted that the cardiac rate became increased, at times to over 200. The neck was enlarged, and the basal metabolic rate, which previously had been plus 19 per cent, became plus 52 per cent. During this period of thyrotoxicosis the myasthenic symptoms disappeared, and no medication was required. Three series of roentgen irradiations were given, after which the pulse rate decreased to 90, the basal metabolic rate to plus 19 per cent, and the thyroid gland became smaller. At this time some myasthenic symptoms reappeared, so that the use of prostigmine was again necessary.

Thorner believes that this case demonstrated a physiologic antagonism between hyperthyroidism and myasthenia gravis. He selected another case of myasthenia gravis and administered thyroid. The evidences of myasthenia were reduced; the basal metabolic rate rose from plus 5 to plus 22 per cent, and the pulse rate to 120. After appearance of irritability, palpitation and excessive perspiration the use of thyroid was discontinued, as there was little therapeutic justification for the continuance of artificial hyperthyroidism.

No conclusion was drawn regarding the use of thymus extract and the possible thyroid-thymus relationship. In 50 per cent of cases of both exophthalmic goiter and myasthenia gravis some abnormality of the thymus gland is found. In the former there may be persistence or simple hyperplasia of the thymus, whereas in the latter thymic neoplasms of various types are found. The lymphorrhages which are present in the muscles in cases of myasthenia gravis were also present in 8 of 9 reported cases of exophthalmic goiter. Ocular palsy is rare in cases of exophthalmic goiter but is common in those of myasthenia gravis. Thorner concludes that the extreme rarity with which these two diseases coexist and the

presence of a type of "seesaw" balance between them appear to support the hypothesis that they are mutually antagonistic. He does not believe that this relation is of immediate therapeutic importance. BECK, Buffalo.

THE MYOGRAM IN TABES DORSALIS AND IN DEMENTIA PARALYTICA. H. KRÄMER and G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **149**:117, 1939.

Krämer and Schaltenbrand describe the result of application of Schaltenbrand's method of mechanical myography in cases of tabes and dementia paralytica. Their chief problem is the investigation of hypotonia, which they believe is not as common even in clearcut tabes as one might believe. They find that even with absence of deep reflexes a number of tabetic persons show a normal myogram. Some other tabetic patients show "anisotonia," or a shift of the middle, relaxed position of the limb toward extension.

The majority of the patients with dementia paralytica or dementia paralytica with tabetic features had no hypotonia, but rather exhibited rigidity or spasticity, though the latter group had areflexia in the legs.

Krämer and Schaltenbrand believe that the absence of myotatic reflexes is not a sufficient explanation for the hypotonia of muscles in tabes. Sherrington's studies were practically all carried out on decerebrate preparations, and nothing is known about the muscle tonus of the intact animal. The authors do not present an explanation of their own, but suggest that cachexia or other trophic disturbances in the muscle following long-lasting absence of reflexes may be responsible for hypotonia. Absence of tendon reflexes, on the other hand, is not evidence of complete interruption of the reflex arc. They quote Nonne, who saw tendon reflexes reappear in a tabetic patient who subsequently had hemiplegia.

Rigidity and spasticity ought not to be surprising findings in a widespread disease such as dementia paralytica, in which the basal ganglia, as well as the pyramidal tracts, have been found to be involved. HOEFER, New York.

Special Senses

ALLERGIC VERTIGO. L. H. CRIEP, Pennsylvania M. J. **43**:258 (Dec.) 1939.

Criep believes that the incidence of labyrinthine vertigo of allergic origin is greater than is suspected. The pathophysiologic basis is in all likelihood edema of the various structures of the internal ear. The symptoms depend on which of these structures is edematous. The diagnosis of allergic vertigo is based on the absence of other etiologic factors, the presence of a family history of allergy, the presence of associated allergic manifestations (such as asthma, hay fever and eczema), a history of clinical sensitivity, eosinophilia, positive cutaneous reactions and/or the response to epinephrine therapy. Vertigo of allergic origin may occur either as an isolated symptom or in conjunction with a series of other symptoms, such as tinnitus, deafness and gastric manifestations. During the attack the patient may break out in a cold sweat. The attack may be preceded or accompanied by nausea and vomiting. Tinnitus may be unilateral or bilateral and is as a rule high pitched. Hearing is usually partially and temporarily impaired, returning to normal in the interval between attacks. Labyrinthine vertigo may result from causes other than allergy: infections, tumors, toxemia or hemorrhage in the internal ear or cerebral centers. The pathophysiologic cause of allergic headaches is thought to be edema of the meninges. Many patients complain of severe dizziness coincident with the headaches. The vertigo of these patients may likewise be the result of an edematous process of the membranous labyrinth. Adequate treatment is predicated entirely on a correct diagnosis. After all possible causes of vertigo are eliminated, the patient should be subjected to an examination for allergy. Based on information elicited from such an investigation, suitable changes can be made in the patient's diet and environment. Hyposensitization, whenever indicated, is undertaken. J. A. M. A.

MACULAR LESIONS IN YOUNG PATIENTS. E. REDSLOB, Ann. d'ocul. **176**:738 (Oct.) 1939.

Redslob finds that hemorrhages in the macula are of relatively frequent occurrence in children 9 years of age or older. The cause is unknown. The condition occurs in patients who are healthy, but who reveal fragility of the vessels. The hemorrhages are not destructive and do not cause much disturbance in vision. They neither produce a central scotoma nor affect the color sense. Occasionally, they have been discovered during refraction in patients with a slight correction and normal visual acuity. The layer of blood is rather thin. However, it is absorbed slowly and leaves small patches, of chamois color, with pigmented or yellow spots, which are often imperceptible. These lesions are not associated with Behr's macular heredodegeneration or with Vogt's cystoid degeneration.

BERENS, New York.

LEBER'S DISEASE CURED BY NEUROSURGICAL INTERVENTION. PUECH, BONNET and GUILLAUMAT, Ann. d'ocul. **176**:755 (Oct.) 1939.

Puech, Bonnet and Guillaumat report the case of a young man with retrobulbar neuritis following whooping cough. Various treatments were attempted, but failed. The etiologic factor was revealed by the fact that the mother and uncle suffered from Leber's disease and had similar ocular symptoms. Neurosurgical intervention revealed that the optic nerves and the chiasm were enclosed in a group of adhesions; these were destroyed. Visual recovery was obtained. The authors compare the condition in this case with optochiasmatic arachnoiditis and stress the importance of early operation.

BERENS, New York.

Diagnostic Methods

THE DAVIES-HINTON TEST OF THE SPINAL FLUID. HAROLD H. MARQUIS, Am. J. Syph., Gonor. & Ven. Dis. **23**:738 (Nov.) 1939.

Marquis attempted to evaluate the reliability of the Davies-Hinton test and to compare it with the Wassermann test of the spinal fluid. When Davies modified the Hinton flocculation test for use in diagnosis of neurosyphilis, he found that the reaction in his test on the spinal fluid correlated with the Wassermann reaction in 90 per cent of cases. Whenever disagreement occurred, the neurologic and hematologic findings were reviewed, and Davies concluded that the results of the modified Hinton test agreed with the clinical diagnosis more frequently than did the Wassermann reaction. Marquis performed the Davies-Hinton and Wassermann tests on 200 consecutive patients on whom spinal puncture was performed. The reactions were in complete agreement in 95 per cent of cases. The laboratory data were correlated with the clinical findings. It was concluded that the Davies-Hinton test on the spinal fluid is a sensitive and reliable test for neurosyphilis, and that when used in addition to the Wassermann test it is of great value, each test serving as a check on the other.

BECK, Buffalo.

THE HUMAN ELECTROENCEPHALOGRAM. M. BALADO, L. ROMERO and J. NOISEUX, Arch. argent. de neurol. **20**:215, 1939.

Balado, Romero and Noiseux employed a six channel amplifier, each channel being condenser-coupled, while the cathode side was grounded and was used for the indifferent electrodes attached to the ears. They recorded by means of Siemans' oscillographs, the six beams being projected onto the same film. The shielding was elaborate and undoubtedly adequate. In cases of epilepsy the authors found that there is no characteristic wave form that distinguishes this condition from other lesions affecting the cortex. In some cases they found no evidence of electrical disturbance, while in others they were able to localize lesions that could not be localized clinically or by means of pneumoencephalograms. In cases of

tumor they described two types of abnormal waves of very large voltage that may be slow, although, owing to blocking of the amplifier, they were not sure of the frequency, and others of moderately elevated voltage and a frequency ranging up to about 100 per second that appeared in groups. Between these two types they found many transitions. They were unable to demonstrate any change in electrical activity in cases of chronic subdural hematoma or extracerebral-intradural tumor. They believe that areas of the cortex that have lost all function have no intrinsic activity but transmit electrical disturbances from neighboring areas. Tumors that do not affect the cortex do not cause any change in the electroencephalogram.

Their conclusions are: (1) Waves of cortical potentials may be recorded through the scalp and skull in a well localized manner. This is due to the high impedance of the cerebral zones around the area from which the waves are recorded. (2) In man these waves have no characteristics that distinguish the different cytoarchitectonic fields. (3) The frequency, phase and amplitude of the waves may be profoundly modified by many things, such as the method of grounding, the placing of the electrodes, the type of amplifier circuit and the recording of waves from other areas transmitted via the association pathways. (4) The presence or absence of bone makes no difference in the electroencephalogram. (5) The disappearance of cortical waves during mental activity and sensory stimulation is not a constant phenomenon, but is variable and depends on many factors, including the part of the cortex examined and the type of amplifier used. (6) Increase or decrease in the frequency of the waves within certain limits has no pathologic significance. (7) Increase in the frequency to between 30 and 50 per second, accompanied by an increase in the potential to about 60 millivolts, has pathologic significance. (8) Decrease in the frequency to 1 or 2 per second accompanied by an increase in potential to from 100 to 200 millivolts has pathologic significance. (9) Changes in waves, as noted in 7 and 8, indicate that at the point where they are found there is an acute or a subacute lesion of the cortex. The lesion may be due to trauma, cicatrix or progressive neoplastic invasion. (10) The changes in the waves noted in 7 and 8 may correspond to the *Krampfströme* of Kornmüller and Tönnies. (11) Pathologic waves have a localizing value of great importance when well recorded and may be useful in neurosurgical procedures. (12) Old lesions do not reveal alterations in the electroencephalogram, except in the difficulty in modifying the waves by means of grounding associated areas.

NORCROSS, San Francisco.

Basal Ganglia

NEUROLOGICAL SEQUELAE OF KERNICTERUS. G. M. FITZGERALD, J. G. GREENFIELD and B. KOUNINE, Brain **62**:292, 1939.

Kernicterus is a disease the acute phase of which is a well recognized clinical entity. It frequently affects several children in the same family. The child is normal at birth, but within the first three days shows severe jaundice. Within twenty-four hours there is evidence of involvement of the nervous system, characterized by tonic and clonic movements, hypertonia and opisthotonos. Children affected usually die within five days. Pathologic examination in cases of the acute phase reveals that certain nuclei of the brain are specifically involved. These areas are stained deep yellow, and the cells in the pigmented areas are glassy and homogeneous, with a tendency toward cytolysis. The structures most frequently affected, in the order of severity, are the subthalamic nuclei, the basal ganglia, the cornu ammonis, the inferior olive, the dentate nucleus, the thalamus and some nuclei of the cranial nerves in the medulla. The jaundice has been variously attributed to a blood dyscrasia, with increased destruction of blood elements, to intoxication of hepatic origin, to fetal septicemia and to maternal toxemia. The first of these causes seems most probable.

The specific localization of the destructive process in the brain appears to depend on some characteristic of the cells or the blood supply of specific areas. Experimentally, it has been shown that areas of the brain which normally contain

iron are most susceptible to anemia, from whatever cause, and to intoxication from bile pigment or manganese. It is suggested that in kernicterus the primary factor is maldevelopment of some degree, while the localization depends on the relative ischemia of the affected areas.

A few cases of kernicterus have been reported in which the patients survived the acute illness. The authors report 3 such cases, in 2 of which there were pathologic studies. The essential features were identical in all the cases. There was a history of severe neonatal jaundice, and in many cases several siblings were affected. Onset of the jaundice was followed rapidly by such nervous symptoms as tonic and clonic movements, rigidity and opisthotonos, alternating with flaccidity. Later, and usually within the first four weeks, choreoathetoid movements appeared. As the child grew older, there developed emotional instability, mental retardation and inability to hold up the head. Pathologically, the same regions observed to be pigmented in the acute stage of kernicterus were involved in the chronic. In the more affected areas loss of ganglion cells and demyelination have consistently been observed.

In view of the anatomic similarity of kernicterus and such disorders as Wilson's disease, Hallervorden-Spatz disease and idiopathic forms of dystonia musculorum deformans in children, it seems important in cases of disorders of the latter group to seek carefully for a history of neonatal jaundice as a possible etiologic factor.

MASLAND, Philadelphia.

CHOREOATHETOSIS AND INFRACORTICAL NERVOUS MECHANISMS. W. F. MENZIES, J. Ment. Sc. **85**:763 (July) 1939.

Menzies' interest in choreoathetosis was aroused when 2 children were brought to the hospital with a condition which seemed to be different from the usual form of choreoathetosis. The patients, a boy and a girl, were unusual in that (1) they were of moderately high mental grade and did not deteriorate mentally as they grew up; (2) the irregular and uncontrolled jerks and spasms were, as far as they could be analyzed, largely representative of ordinary normal subcortical patterns; (3) there was at first no spasticity, and even after ten years there was shown only slight stiffness of the ankles and toes, with foot drop; (4) epilepsy was absent, and (5) there was no evidence that sensation was involved. The patients were observed for ten years. The boy died; the brain showed striking changes in the substantia nigra. The putamens showed definite mottling, suggesting status marmoratus. The most striking involvement was in the substantia nigra on both sides, but to a greater degree on the left. The whole length of the zona compacta disclosed loss of the large ganglion cells; of those remaining, a few contained some melanin, but none, as far as could be judged, a normal amount. Some cells were mere ghosts, although the outlines of the nucleus, apparently of normal shape and size, remained visible; many others showed swelling or loss of Nissl substance. Melanin was seen in capillaries and scavenger cells. Throughout the substantia nigra there was dense gliosis, so that it was not easy to be certain about the fibers; apparently, however, there was a great increase of fine nonmyelinated fibers, not all of them being glial; many were in thick strands, digitating into the crura. It was impossible to follow either the axons from the basis pedunculi or those entering the tegmentum. Examination of the pontile region disclosed no abnormality of myelin or glia; there was no observable loss of cells. The changes in the putamen and the substantia nigra were the only ones of importance. The second patient, the girl, has shown gradual improvement; when she was 17 secondary sex characteristics developed, without, however, a gain in motor control. She probably will never be able to walk.

On the basis of his findings, and with a good deal of speculation, the author concludes that the substantia nigra is one of the chief centers for coordination of voluntary and automatic muscular action, the spasm being energized by the emotional discharge of epinephrine through sympathetic outflow from the hypothalamus.

KASANIN, San Francisco.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

H. Douglas Singer, M.D., *President, in the Chair*

Regular Meeting, Oct. 5, 1939

Sigmund Freud. Dr. Franz Alexander, Chicago.

This article was published in full in the March 1940 issue of the Archives, page 575.

Metabolism of the Brain Before and After Insulin and Metrazol Treatment, as Determined by the Oxygen and Carbon Dioxide Contents of the Blood. Dr. M. K. Horwitt and Dr. Erich Liebert, Elgin, Ill., and Dr. George A. Wiltrakis, Chicago.

No information is yet available regarding the utilization of oxygen by the brain after a course of insulin or metrazol treatments. Any change in the metabolism might find its expression in an increased uptake of oxygen from the blood. The present investigation was undertaken to observe whether any change in the gaseous constituents of the blood could be observed before and after these treatments.

The technic described by Myerson and Halloran (*Am. J. Psychiat.* **10**:389, 1930) was used to obtain samples of blood. These samples were drawn, at intervals of approximately six weeks, before, during and after treatment. Comparison of the data obtained recalled no significant changes.

The results do not necessarily disprove the theory that the current therapies for schizophrenia are efficacious because they increase cerebral respiration, since many factors, such as rate of blood flow and blood volume, may be involved in an alteration of brain metabolism even though the gaseous content of the blood remains unchanged.

It is concluded that examination of the oxygen metabolism of the brain by studying the carbon dioxide and oxygen contents of arterial and internal jugular venous blood does not supply information which would indicate a change in gaseous metabolism either in patients who had benefited from insulin or metrazol therapy or in those whose condition was unimproved.

DISCUSSION

Dr. Franz Alexander, Chicago: I wish to ask about the technic employed in this study. I did work many years ago on the total consumption of oxygen in the brain and remember the difficulties of such determinations only too vividly. What is of interest, of course, is not the difference in concentration of gases between the incoming arterial and the outgoing venous blood. This alone does not mean anything if one does not also know the total volume of blood which goes to the brain. The latter is variable, and slight differences in the speed of blood flow make a tremendous difference in the results, even though the difference in concentration of gases between the arterial and the venous blood may remain the same. The actual oxygen consumption and carbon dioxide production in the brain tissue are the chief interest. My question is: How, in this investigation, was the rate of the blood flow taken into account?

From the internal jugular vein one does not obtain blood which comes from brain tissue alone. One cannot be sure what structures have derived their oxygen from this blood. Taking blood from a sinus would be a more correct method.

Whether this is practicable I do not know. Certainly it can be done in animal experimentation.

DR. M. K. HORWITT, Elgin, Ill.: We are glad that Dr. Alexander agrees with our observations on the difficulties of evaluating the gaseous content of the blood in the absence of information on blood flow and blood volume. There have been several reports indicating that the gaseous metabolism of schizophrenic persons differs from that of normal subjects, and that this difference can be observed by studying the changes in the oxygen and carbon dioxide content of the blood. This investigation was initiated to verify, and if possible, to extend and apply this observation.

With regard to Dr. Alexander's question concerning the possibility of obtaining blood from the superior sagittal sinus rather than from the jugular vein, it does not appear that the advantages of such a technic would compensate for the difficulties attendant on trephination.

DR. GEORGE A. WILTRAKIS, Chicago: I may add that in this study we followed the procedure of internal jugular and brachial venous punctures suggested by Myerson. The internal jugular venous punctures were made high in the neck, at the level of the tip of the mastoid bone. For practical purposes, the blood thus obtained can be considered as venous blood from the brain. There is added to it, above the level of the mastoid, only a small amount of blood from the cochlear vein and from small veins from the nose.

To obtain blood direct from the sinuses, as by trephination and aspiration from the superior sagittal sinus, would be a complicated and dangerous procedure in adult human subjects. In experimentation on animals this might be desirable.

Direct Psychotherapy of Children. DR. MAXWELL GITELSON, Chicago.

This article is published in this issue of the ARCHIVES, page 1208.

H. DOUGLAS SINGER, M.D., *President, in the Chair*

Regular Meeting, Nov. 2, 1939

Use of Fantasy Tests in Differential Psychiatric Diagnosis. DR. JULES H. MASSERMAN, Chicago, and DR. EVA R. BALKEN, Chicago.

During the past three years we have been investigating the fantasy productions of patients in the psychiatric division of the University of Chicago Clinics by means of a special method. We hoped this method would permit a relative freedom of fantasy, but at the same time render possible a searching analysis and a point to point recording and comparison of the fantasy material.

Technic.—The patient was informed that he was to have an opportunity to display his literary ability, his facility in imagination or his skill at story telling, or was given such other assurance as seemed best calculated to diminish his defenses and secure a relatively free flow of fantasy. The patient was then presented with a series of twenty Morgan-Murray test cards, and was asked to tell a story about the people or the situation he fancied he saw in each of the pictures and to carry his narrative through to any conclusion he desired. Verbatim records were taken of the productions, but no limitations were placed on his fantasies or on the time taken to tell them. A single test session, covering perhaps only ten pictures, would last from one to three hours. The test was if necessary continued the next day. Except for a certain dolorousness, the pictures are relatively neutral. In other words, they can suggest a great variety of dramatic or other situations—the nature of the imagery obviously depending on whatever special interpretation of each picture is evoked in the subject.

Results.—When confronted with the pictures in the test situation, a patient reacts by several interesting mental mechanisms. These take the form of imaginary projections, which assume three primary dimensions: (1) The patient peoples his fantasy with characters so designed that each represents a different aspect of, or force in, his own personality; (2) he places these imaginary personages in situations that symbolize his own conscious or unconscious intrapsychic conflicts, and (3) he resolves the dramas he himself has so conjured up in ways indicative of the solutions he unconsciously seeks for his own emotional difficulties.

Unfortunately, we cannot substantiate the validity of this approach by citing from detailed case reports, but the disguised wish-fulfilling functions of the fantasies may be illustrated by a brief clinical example: A middle-aged matron of a rooming house, who already felt insecure in her marriage because of a suspected love affair of her husband with a girl boarder, suffered an exacerbation of an anxiety syndrome when a female relative—whom she outwardly professed to love—came to live in her home. In response to one of the pictures the patient produced the following fantasy: "It might be a landlady finding a dead body or something in her home—only she doesn't look as horrified as you'd expect. The dead body is a roomer who committed suicide. The landlady is worried, though, because it happened in her house."

Without any deep interpretations, I believe it can be stated that this fantasy revealed the patient's unconscious wish for the death of her fancied rival, and also a desire to be absolved from guilt and responsibility by calling the death a suicide and by professing embarrassment that it occurred in her home. Because of the same unconscious defenses, the patient recognized no immediate connection between her fantasies and her actual life situation, although such a relationship was evident in many of her stories. In similar ways the fantasies of this and other patients plainly indicated the transference relationship, the resistances to and the effects of psychotherapy, and the prognosis as conditioned by the unresolved conflicts and anxieties in the individual case.

Use of Fantasies in Differential Diagnosis.—1. The fantasies of mentally deficient patients showed a definite naïveté of material and dearth of imagery which correlated well with the findings of Hargreaves and Winch indicating that facility and wealth of imagination involve an appreciable amount of the Spearman factor of general intelligence. In contrast, patients of superior intelligence, when not too inhibited emotionally, produced fantasies rich in detail, versatility and creative invention.

2. The fantasies of patients with conversion hysteria were frequently superficial and almost flippant, tended to be frankly sexual in content and often involved persons easily identified as members of the patient's family—in which case, however, the erotic scenes generally ended in frustration. Hypochondriacal tendencies in the patient were often projected in fancy onto the martyred, misunderstood, long-suffering hero or heroine of the story.

3. Patients with marked neurotic anxiety—that is, clinical anxiety states—were characteristically guarded in their productions in response to the presentation of the first few pictures. However, if their shy, uneasy, hesitantly verbalized attempts to win the approval of the examiner were encouraged, they then produced fantasies characterized by moving, dramatic situations and intense, comparatively clearcut conflicts among the characters, although these conflicts were generally made to appear futile and tragic. Moreover, patients with anxiety neuroses often identified themselves directly with the characters in their fantasies, thus giving their stories a frank autobiographic cast.

4. The fantasies of patients with obsessive-compulsive neuroses were characterized mainly by pervading uncertainty—a sort of fruitless, querulous indecision, which sometimes even led the patient to appeal to the examiner to help him with the solution of problems presented in his own fancies. Moreover, in many cases there was frequent recurrence of a few clearly related, almost stereotyped, situations expressive of marked ambivalence in respect to important emotional questions, and these basic fantasies were usually repeated at length and in great detail.

Often the leading character in the fantasy suffered great travail of spirit through no fault of his own and despite his superior intelligence, courage, ability, righteousness and other excellent qualities.

5. The responses of patients with paranoia to most of the pictures were characteristically evasive and guarded, although occasionally a response with a highly significant emotional charge broke through. These patients, moreover, frequently suspected the purpose of the test and often took care to specify that their fantasies were in no sense autobiographic.

6. The fantasies of depressed patients were characteristically halting, retarded, fragmentary and more or less deeply colored with nihilistic ideas of guilt and self depreciation.

7. Certain schizophrenic patients showed apparent inability to construct abstractions, express development or movement, or even go beyond an impersonal, concrete, literal description of the picture. In other cases the fantasies were disjointed and highly bizarre and had little or no relationship to the original picture.

These were the diagnostic generalizations derived from a study of the fantasy material of more than 100 patients. The criteria here outlined, however, were sometimes deficient in three respects, namely: the occasional difficulty of their application, their lack of complete specificity and the possible variations in the subject interpretation by the examiner. To reenforce the nosologic criteria already stated, therefore, an attempt was made to devise supplementary methods that could be applied objectively not only to the symbolic and structural content of the fantasies, but to the very language the patient used in telling his stories.

Analysis of Language.—In order to analyze our material in this light, we selected the fantasies of 15 patients whose illnesses could be classified by all the usual criteria as typical anxiety states, conversion hysterias or obsessive-compulsive neuroses. The language of the fantasies of each of these patients was then analyzed on the basis of over eighty new criteria, of which only ten were finally selected as being most objective and at the same time most significant for the purposes of the present study. The criteria are outlined, with the corresponding analysis of the fantasies, in the accompanying tables. They are briefly defined as follows:

1. The average number of words per fantasy. This is obviously a measure of the length, if not always of the richness, of the productions of the patient.

2. The number of predicative and attributive adjectives, indicating the relative wealth of static description in the fantasy.

3. The relative number of active, passive and intransitive verbs; as will be shown, a large amount of verbal action was found to connote a kinetic release in fantasy of marked libidinal tensions and anxiety in the narrator.

4. The relative frequency of positive or negative forms of expression in the fantasy, designated as "pro" and "con" statements. The "pro" forms indicate the ability of the subject to make fairly straightforward, positive statements in his fantasy with apparent emotional equanimity. The "pro" statements can be subdivided according to degree into those of possibility, probability or certainty, as opposed to "con" statements of impossibility, improbability or uncertainty.

5. Expressions in the fantasy of alternatives or equivalences in will or desire, such as saying in relation to the first picture: "The boy wants to become a famous virtuoso but he really hates the violin, and anyhow he doesn't want to give his father the satisfaction."

6. Expressions denoting self-compulsive trends in the patient's thinking which he projects onto his characters. The fantasy then contains statements such as "she finds it necessary," "must," "he is forced" or "she has to."

7. The number of questions asked of the examiner by the patient during the test.

8. Special expressions with various connotations, such as: (*a*) vagueness ("sort of" and "kind of"); (*b*) reasoning ("because"); (*c*) derivation ("as a result"); (*d*) means ("this is how," "he wonders how"), and (*e*) interjections ("well").

9. (*a*) The number of occurrences of the first personal pronoun, and (*b*) direct references to the narrator, such as: "it seems to me"; "the way I see it"; "I think," and "I would say," serving as expressions of the egocentricity of the patient's imagery.

10. Direct identifications of a character in the fantasy with the narrator, such as "this might be me"; "if it were I," or "just like my own story." These expressions were more obvious instances of strong and partly conscious projections of the patient into his own story.

TABLE 1.—*Criteria for Differential Analysis of the Language of the Fantasies of Neurotic Patients*

Type of Neurosis	Conversion Hysteria	Anxiety Hysteria	Obsessive-Compulsive Neurosis
1. Words (average per fantasy)	177	167	213
2. Adjectives (per 100 words)	8.40	4.00	6.55
3. Verbs: Active voice	4.99	4.79	5.47
Passive voice	0.78	0.70	0.56
Intransitive	5.54	6.96	8.17
Total	11.31	12.45	14.20
Verb-adjective quotient (V-Aq)	1.35	3.11	2.17
4. Form of propositions:			
Pro: (*a*) Possibility	0.70	1.45	1.03
(*b*) Probability	0.77	1.69	1.21
Total	1.47	3.14	2.24
Con: (*c*) Impossibility	0.13	0.50	0.78
(*d*) Improbability	0.09	0.27	0.14
Total	0.22	0.77	0.92
Con-pro quotient (C-Pq)	0.15	0.25	0.41
(*e*) Certainty	0.63	0.53	0.45
(*f*) Uncertainty	0.18	0.29	0.67
Certainty-uncertainty quotient (C-Uq)	3.50	1.83	0.67
(*g*) Qualifications	1.25	2.68	3.69
Qualifications-certainty quotient (Q-Cq)	1.99	5.01	8.20
5. Alternatives	0.44	0.76	0.54
6. Compulsions	0.12	0.36	0.36
7. Questions	0.73	0.52	0.12
8. Special expressions: (*a*) vagueness	0	0.73	0
(*b*) reasoning	0.18	0.45	0.57
(*c*) derivation	0.08	0.06	0.32
(*d*) means	0.06	0.02	0.19
(*e*) interjections	0	0.40	0.03
9. (*a*) First person	1.07	2.49	2.63
(*b*) References to narrator	0.16	1.13	1.04
10. Identification with self	0	0.47	0.21

In addition to the single criteria listed, the following indexes, or quotients, were found to have individual significance: A. The verb-adjective quotient (V-Aq). This was obtained simply by dividing the total number of verbs by the total number of adjectives. As has been indicated, high values for this quotient, i. e., a preponderance of verbs in the fantasies, denoted restless, forceful action in the fantasies and indicated a release of marked neurotic anxiety in the subject.

B. The con-pro quotient (C-Pq). This was derived by dividing the number of expressions of impossibility and improbability by the number of expressions of possibility and probability. Low values for this quotient corresponded to smoothness and positiveness of statement and narration with superficial emotional equanimity in the subject, which patients with conversion hysteria often showed.

C. The certainty-uncertainty quotient (C-Uq). This was determined by the proportion of the corresponding expressions.

D. The qualifications-certainty quotient (Q-Cq). This was determined in a manner similar to that for the preceding quotient. The last two quotients stood in reciprocal relationships, but together indicated the presence of obsessive hesitation, doubt and self criticism in the fantasies in reaction to the anxieties mobilized in the narrator.

Briefly, then, analysis by these criteria showed the following differential points in the fantasies of the three groups of patients: In conversion hysteria the characteristics of the fantasies were: productions of medium length, a plethora of leisurely descriptive material with little forceful action (low V-Aq), little ambivalence or qualification of statement (low C-Pq and certainty quotients and low scores for qualifications and alternatives) and a minimum use of the first person and of identifications with the narrator. It is of theoretic interest that this absence of the usual indications of anxiety in the very language of the fantasies, as shown independently of their content, is consistent with the most striking psychodynamic mechanism of conversion hysteria, namely, the abolition of inner anxious tensions by the device of "converting" the repressed erotic or aggressive urges into symptoms which are libidinally gratifying and at the same time self punitive. With his intrapsychic tensions thus autoplastically resolved, the person with a conversion hysteria can then apparently indulge in rich, slow-moving, leisurely fantasies, which exhibit but little action or indecision and which are so lightly charged with projected anxiety that there are in the stories almost no direct references by the patient to his own conflicts. Significant also is the fact that there was a minimum of interpersonal tension in the test situation, as is shown by the number of casual questions the patient felt free to ask of the examiner.

In contrast, the fantasies in the anxiety states were significantly brief, the action was extremely dramatic (highest verb-adjective quotient), alternatives of action were most frequently sought; special expressions denoting vagueness, hesitation and fear were freely used, and direct identification of the narrator with characters in his fantasy often occurred. These characteristics of the language of the fantasies are in agreement with the view that in anxiety hysteria the intrapsychic tension is not relieved either by autoplastic conversion symptoms or by an obsessive-compulsive ritual, and therefore seeks expression in vivid, dramatic, incompletely projected productions. The fantasies, however, are cut short by the anxiety they themselves mobilize and thus leave the fantasied situations as unresolved as the emotional conflicts of the subject.

In obsessive-compulsive states a somewhat similar language syndrome appeared, with the highly characteristic modification that the compulsion (high score on "compulsions") that the patient felt to rationalize and elaborate (by "special expressions") his many ambivalences and uncertainties in his fantasies (highest C-Pq and C-Uq; highest Q-Cq) nearly doubled the average length of his production. Theoretically, these characteristics of expression are, again, in accord with the psychodynamic pattern of the obsessive-compulsive neuroses, characterized by the typical defenses of vacillation, doubt, obsessive rationalizations and ritualistic meticulousness of thought and action. If, however, these defenses fail, anxiety becomes manifest; so it is not surprising that the fantasies of persons with obsessive-compulsive neuroses show a high V-Aq and a high self identification factor, and in other ways manifest the dynamically close relationship of this neurosis with the anxiety states.

Table 2 lists the scores for the various differential criteria, with values for anxiety hysteria rated constantly at 100, and thereby demonstrates with greater significance the differences in the three neuroses. Thus, the discursive fantasies of the patients with obsessive-compulsive neuroses have nearly twice as many words as the short, vivid fantasies of the patients with anxiety hysterias, but the stories the latter tell are much more moving and dramatic, as objectively graded by the verb-adjective quotient. In contrast, the patients with conversion hysteria use a positive, direct mode of narration, whereas the fantasies of the patient with obsessive-compulsive neurosis contain more than five times as many expressions of

uncertainty and qualification. The other criteria, when compared in a similar manner, likewise show obvious and significant differences among the three reaction types.

With regard to this language analysis, however, it must be remembered that other concurrent mental states are not excluded by the criteria applicable to the neuroses; thus, in a separate series of psychoses studied by the same methods, a patient with paranoia with marked homosexual anxiety had a higher V-Aq (6.3) than any patient with anxiety hysteria in the present series; similarly, the fantasies of "depressed" patients with concurrent obsessive-compulsive trends showed many of the features of the latter neurosis. It may be reemphasized, therefore, that, in view of the variability and multiplicity of intrapsychic dynamisms present in every patient, the criteria here outlined remain to be supplemented with others indicative of paranoiac, manic, schizophrenic and other reactions, and that even then only in cases in which dominant psychic reactions in relatively pure form are

TABLE 2.—*Comparison of Scores for Differential Criteria with Those for Anxiety Hysteria Rated as 100*

Type of Neurosis	Conversion Hysteria	Anxiety Hysteria	Obsessive-Compulsive Neurosis
1. Words	165	100	199
2. Adjectives	210	100	164
Verb-adjective (V-Aq)	43	100	69
Con-pro quotient (C-Pq)	60	100	164
Certainty-uncertainty quotient (C-Uq)	191	100	37
Qualifications-certainty quotient (Q-Cq)	39	100	164
5. Alternatives	58	100	71
6. Compulsions	33	100	100
7. Questions	140	100	23
8. (*a*) Vagueness	0	100	127
(*b*) Reasoning	40	100	0
(*c*) Derivation	133	100	533
(*d*) Means	300	100	950
(*e*) Interjections	0	100	8
9. (*a*) First person	43	100	105
(*b*) Reference to narrator	14	100	92
10. Indentification with self	0	100	45

exhibited can the fantasies be said to have a "diagnostic" value in the sense of ordinary psychiatric classification.

DISCUSSION

DR. LEON J. SAUL, Chicago: I think this paper is an important piece of work. The authors have concentrated less on the content of the fantasies than on the formal aspect. That, I think, is of importance in tying up psychologic investigations with linguistics, in which some analysts, for instance, Freud, in his paper on the "Antithetical Sense of Primal Words," have expressed interest. Hitschmann made a study of dreams of persons with compulsion neuroses and psychoses and compared the types of dreams in much the same way as Dr. Masserman and Dr. Balken have compared the contents of the responses to the Murray pictures. It occurred to me that such a formal study of certain aspects of the dream might be illuminating, and I wish to ask whether Dr. Masserman and Dr. Balken have done anything in this direction.

DR. EVA R. BALKEN, Chicago: In answer to Dr. Saul, I may say that dreams will yield to the same type of language analysis as the fantasies. Unfortunately, dreams are seldom recorded verbatim, and a verbatim record of the fantasies is

an essential element of our language analysis. However, we analyzed the poetry and dreams reported in Dr. Harry B. Levey's article, and found that the verb-adjective quotient was greater in the excerpts in which there was shown to be a quantum of anxiety.

DR. JOSEPH C. RHEINGOLD, Chicago: I wish to ask Dr. Masserman whether the test has been used diagnostically in advance of classification by the usual methods, or whether its use has been limited to correlation with diagnoses already established.

DR. A. A. LOW, Chicago: The neatness with which the figures in the authors' tables match their clinical observations is a trifle disturbing. According to the tables, they must have dealt with clearcut conditions of hysteria, on the one hand, and with anxiety and compulsive states, on the other. However, such clearcut syndromes are seldom seen. Hysterical patients have a considerable mixture of obsessive-compulsive phenomena, and vice versa. An attempt to draw diagnostic inferences from the speech productions of patients meets with various difficulties. If a person says: "I ought to visit John" or "I think I have to visit him," the "ought" and "have to" do not necessarily refer to a sense of being compelled. It would be hazardous to range verbal expressions of this kind under the heading "compulsion phenomena."

I wish to ask Dr. Masserman whether studies were made on control subjects.

DR. JULES MASSERMAN, Chicago: As Dr. Saul suggests, there are interrelated two methods of interpreting our material: first, by regarding the fantasies as day-dreams and interpreting their intellectual and affective symbolisms from the standpoint of unconscious motivations, and, second, by analyzing the structure and content of the language employed to express each fantasy. The first method was reported in a previous clinical communication; the second, and perhaps the more objective, method was more specifically dealt with in this paper.

Dr. Rheingold's question was, I believe, anticipated in the portion of the paper concerned with the meaning and significance of a psychiatric "diagnosis." Granted that absolutely pure psychiatric reaction types are as rare as absolutely pure chemical substances, one can, nevertheless, learn a good deal about how the ideally pure substance behaves by investigating impure solutions of it. Incidentally, we searched our files of hundreds of cases before we selected patients with the relatively manifest neurotic patterns used in this study. However, since each group showed an inner consistency in tests without criteria and differed in significant respects from other groups, our method assumes a neuristic validity.

Finally, Dr. Low's query about "normal" subjects must be considered. It would, of course, be a sophistry to request Dr. Low to select a group of subjects that he could certify as "normal" for testing purposes, but it must be emphasized that our method deals with dynamics of personality organization, for which there is no accepted median. Personality traits are called "neurotic" only when they reach extremes of external expression. The fantasies of any one of us might not reveal any "abnormality," but would nevertheless, I dare say, be significant.

Anorexia Nervosa. DR. H. W. BROSIN, DR. WALTER L. PALMER and MR. DAVID SLIGHT, Department of Medicine, University of Chicago.

As many cases of anorexia nervosa are explained on the basis of disease of the pituitary gland (Simmonds' cachexia), the etiology, course and response to various therapeutic measures have been studied in 24 cases. The physical and psychiatric status, laboratory findings and differential diagnosis were also considered. Anorexia nervosa is only a symptom found in many conditions of the reaction type; most of these conditions are mild psychoneuroses or reactive depressions. Evidence of a borderline psychosis was found in certain cases in which the condition was obdurate to treatment. These cases were described in detail. This differentiation is valuable for estimating both prognosis and methods of treatment. Limitations of various therapeutic methods were discussed.

Psychologic Settings of Attacks of Urticaria. Dr. Leon J. Saul, Chicago.

A woman was referred for psychoanalysis by an allergist because of severe urticaria. A thorough examination for allergy had given negative reactions; on the other hand, she was clearly upset emotionally. It was found that the attacks of urticaria occurred consistently when longings for her parents, chiefly her father, were aroused and frustrated. This was demonstrated by a review of the life circumstances and dreams in connection with each of her attacks. The findings were supported by observation of other cases.

DISCUSSION

Dr. Henry W. Brosin, Chicago: I wish to ask about the criteria for the choice of the symptoms of urticaria, or the factors which determine the choice.

Dr. Thomas M. French, Chicago: I wish to add two observations based on a case of neurodermatitis in which findings were similar to some in Dr. Saul's case. In my case there was the relation between crying and the cutaneous symptoms that Dr. Saul speaks of. The patient was suffering from severe neurodermatitis, and I never saw a girl who showed a more intense picture of impatient weeping. The crying did not come on immediately, but only after a rather friendly relationship had been established at the psychiatric interview. Then there came a flood. When seen a week or so later, the patient reported marked improvement in her cutaneous symptoms, due possibly in part to the relief of tension achieved by her crying. The second feature in which this case resembled that of Dr. Saul was the strong attachment to the father and the intense jealousy of an older sister. The patient experienced severe exacerbations of dermatitis after marriage, in which there was considerable frustration on account of her sexual inhibitions. In Dr. Saul's case, also, there were both stimulation and frustration. It is this combination of stimulation and frustration that I regard as the most specific dynamic constellation for conditions of the skin in which itching is a prominent feature. I doubt whether merely frustrated, dependent cravings are so important. I believe this sort of reaction requires two factors, intense stimulation and frustration of a strong craving being in my opinion the etiologic factor.

Dr. Leon J. Saul, Chicago: I cannot answer Dr. Brosin's question as to why the skin was selected. Two possibilities I may mention: One, which has been discussed in the literature, is the predominance of exhibitionism in many cases of cutaneous lesions. The other is the "watery" nature of the material when this patient first came under observation. She told of enuresis, of being held under water by her father; that may have had something to do with the urticaria. I think there is no fundamental disagreement with what Dr. French has said. Probably it is a quantitative matter. Intense stimulation and frustration of the strong craving which has been aroused may be a factor.

PHILADELPHIA NEUROLOGICAL SOCIETY

Temple Fay, M.D., *President, in the Chair*

Regular Meeting, Oct. 27, 1939

New Methods of Treatment of Migraine: Preliminary Report on Vitamin B_1 Therapy. Dr. Harold D. Palmer.

Review of Recent Treatments.—Briefly, the advances in the field of migraine during the past few years have taken five distinct lines: (1) a study of allergy, chiefly as related to food substances; (2) a study of the mechanism of headache, with special reference to the sympathetic nervous system and vasomotor phenomena in migraine; (3) a study of endocrine factors, both as direct and as contributing

causes; (4) the development of more or less specific remedies, of which ergotamine tartrate is now perhaps the most widely used; (5) the introduction of surgical procedures intended to control the pain by anesthetization of local areas of the face and scalp and to control the vascular changes by ligation of cranial vessels.

The allergic theory is important in any concept of the cause of migraine. Scarcely any patient suffering from this disorder fails to list a series of substances which he believes to be a direct cause of or substantially contributory to his migrainous troubles. In the 24 cases summarized in this paper, the most common offenders were sea foods, milk, eggs, cheese, mushrooms, beer, rye whisky, wheat, chocolate and strawberries. In the same way, many patients have listed other apparent causative factors, such as constipation, emotional shock, nervous strain, fatigue, exposure to wind and blinding sunlight. One of the best summaries of the relationship of allergy and migraine is that by Hartsock and McGurl (*M. Clin. North America* **22**:325, 1938). They expressed the belief that the inherited tendency to migraine is definite. Edema and spasm of the smooth muscles, the chief characteristic of allergy, could readily explain the symptoms of migraine. Furthermore, many patients have observed their own attacks sufficiently to be able to trace the origin to the ingestion of certain foods. The portal of entry is undoubtedly the gastrointestinal tract. Certain disturbances of the gastrointestinal tract would permit absorption of the offending protein molecule more readily than others, and these conditions are more apt to be present when the patient is fatigued or emotionally upset. The migraine syndrome has also been observed to have a direct relation to mechanical duodenal stasis, and some relief has been obtained by its correction. Hartsock and McGurl stated that 30 per cent of patients with migraine secure complete relief so long as they avoid the allergens to which they are sensitive; in this group are included only patients who find the routine sufficiently easy to permit complete cooperation in following instructions. Some benefit is obtained by 45 per cent of patients; this heterogeneous group secures partial relief, i. e., a decrease in the frequency or severity of the attacks or both; 25 per cent fail to respond to specific diets for control of allergy.

Wide experience in testing for allergens has shown that there is no strict agreement between the allergic reactions to food known to the patient by experience and the findings in cutaneous tests. Tuft (*Pennsylvania M. J.* **39**:162 [Dec.] 1935) expressed the belief that cutaneous tests properly carried out and correctly interpreted may be of great value in many cases. However, the cutaneous reactions to foods, as compared with those to other types of allergens, may be slight, or even negative, in cases in which a definite clinical reaction to these foods is obtained.

Foster Kennedy (*New York State J. Med.* **36**:469 [April] 1936) found that 69 per cent of 63 patients with "allergic headache" improved when on a restricted diet. Winkelman and Moore (*Tr. Am. Neurol. A.* **63**:150, 1937) stated that allergy is under parasympathetic control, and stated the belief that migraine headache is due to localized edema of the brain resulting from allergic sensitivity to foods and that the mechanism is similar to that of asthma. Emotional factors may cause the autonomic nervous system to augment the existing allergic reaction. Vaughn (The Practice of Allergy, St. Louis, C. V. Mosby Company, 1939) and Rowe (Food Allergy, Philadelphia, Lea & Febiger, 1931), recognized authorities in the field of allergy, stated that the relationship of allergy and migraine is clearcut; both authors cited striking improvements with carefully managed diets for relief of allergy. Földes (*Am. J. Digest. Dis. & Nutrition* **1**:359 [Aug.] 1934) has devised an "anti-retentional" diet, based largely on the theory of dehydration. The diet is rich in protein and restricted in carbohydrates, with a moderate allowance of fat. Moderate limitation of salt, restriction of liquids and the use of laxatives are also recommended. He reported marked improvement in patients with migraine and suggested the "antiretentional diet" as a diagnostic test for migraine.

The mechanism of headache, with special reference to types of migraine, has been studied by Graham and Wolff (*Tr. Am. Neurol. A.* **63**:164, 1937) and Wolff and Sutherland (*ibid.* **64**:103, 1938). The actual mechanics of the vasomotor system has been examined during migraine headache, and is at least partially understood. The data show that the pain in migraine is due to the stretch of relaxed arterial walls. The termination of a migraine headache by ergotamine tartrate and by other vasoconstricting substances parallels a decline in the amplitude of pulsations of the cranial arteries. Ergotamine tartrate produces a decrease of as high as 84 per cent and an average decrease of 50 per cent in the amplitude of pulsations of the temporal arteries when administered during a migrainous headache. There is a direct relationship between the amplitude of pulsation of the cranial arteries and the severity of the headache. Histamine phosphate increases the amplitude of the pulsation and the severity of the headache. Graham and Wolff concluded that migraine is an expression of dysfunction of the cranial vascular bed, probably dilatation of certain branches of the external carotid artery. They did not venture a theory as to the cause of the process. Fay (Mechanism of Headache, ARCH. NEUROL. & PSYCHIAT. **37**:471 [Feb.] 1937) showed that stretch of the cerebral vascular tree produced headache and that dehydration (by means of reduced carbohydrate intake and restriction of fluids) brought about some relief. Fay expressed the belief that there is an ischemic, as well as a hyperemic, stretch and that both processes may give rise to headache.

In the field of endocrinology Timme (*A. Research Nerv. & Ment. Dis., Proc.* [1936] **17**:572, 1938) demonstrated a hypophysial factor in certain cases of migraine and showed that actual change in the bone or distortion in the region of the sella turcica can be found in a high percentage of cases of migraine. O'Sullivan (*Endocrinology* **24**:414 [March] 1939), in a general discussion of migraine therapy, emphasized the value of endocrine substances in certain cases. Glass, Catchpole and McKennon (*Endocrinology* **20**:333 [May] 1936) found ovarian deficiency in association with migraine. They demonstrated increased amounts of the follicle-stimulating principle and decreased amounts, or absence, of estrogen in the blood and urine of women with migraine. They reported that administration of estrogenic substances was successful in 80 per cent of cases. The theory is that estrogen, which is antagonistic to the follicle-stimulating principle, reduces the dysfunction and brings about normal endocrine balance. Disordered menses became regular with this form of therapy. Relapses occurred after estrogenic therapy was stopped. Administration of a preparation containing the gonadotropic principle from the urine of pregnant women was found to aggravate the headaches. Numerous other contributions in the last two or three years have dealt with the success and failure of endocrine therapy.

The introduction in 1935 of ergotamine tartrate into general use was followed by reports of success in a high percentage of cases. Lennox and von Storch (Experience with Ergotamine Tartrate in 120 Patients, *J. A. M. A.* **105**:169 [July 20] 1935), Brock and his associates (*Am. J. M. Sc.* **188**:253, 1934), Soltz and his co-workers (*Bull. Neurol. Inst. New York* **4**:432 [Dec.] 1935) and others have obtained relief in nearly 90 per cent of cases of migraine headaches by oral, intravenous or subcutaneous administration. Recent statistics have reduced this favorable record to approximately 70 per cent. There is no doubt that prompt and gratifying relief is produced in many cases by the use of this drug. However, pure statistics reporting "relief" are likely to be somewhat misleading; in the analysis of therapies in this paper some of the untoward reactions will be enumerated. The limitations of ergotamine tartrate therapy have been discussed by von Storch (Complications Following the Use of Ergotamine Tartrate, *J. A. M. A.* **111**:293 [July 23] 1938). In 189 migrainous patients treated with ergotamine tartrate, the most commonly observed accessory symptoms were nausea, vomiting, numbness and tingling of the hands and feet, muscular pains and muscular stiffness. It was recommended that nausea and vomiting produced by the drug be relieved by the administration of 0.4 to 0.5 mg. of atropine sulfate. Numbness and tingling

in the extremities constitute a warning of impending arterial thrombosis only if they are prolonged and accompanied by great pain. Other symptoms, such as choking sensations, globus hystericus, insomnia, restlessness, substernal oppression, precordial pain and femoral or brachial perivascular pain, occur less frequently and, although somewhat alarming to the patient, appear to constitute hazards of minor character only.

Inhalations of oxygen have been recommended for the relief of migraine, but wide use of them has not been made. They are thought to be at least an aid in aborting some of the seizures.

The surgical procedures which have been used in attempts to relieve migraine are ligation of the middle meningeal artery, cervicothoracic sympathetic ganglionectomy and trunk resection, injections of alcohol in the supraorbital or infraorbital nerve, removal of the stellate ganglion and section of the trigeminal nerve. Craig (*Proc. Staff Meet., Mayo Clin.* **10**:362 [June 5] 1935) and Critchley (*Brit. M. J.* **2**:794 [Oct. 26] 1935) cited instances of relief from several of these procedures.

TABLE 1.—*General Data in 24 Cases of Migraine*

Age at Onset		Duration of Migraine		Days of Headache per Month		Hereditary Factors for Migraine in Family History	
Age	Cases	Years	Cases	Days	Cases	Relative	Cases
5 to 10	4	5 to 10	3	1 to 5	3	Sister	4
10 to 15	5	10 to 15	7	5 to 10	9	Brother	1
15 to 20	7	15 to 20	4	10 to 15	7	Mother	13
20 to 25	3	20 to 25	2	15 to 20	3	Father	4
25 to 30	3	25 to 30	2	20 to 25	2	Maternal aunt	5
30 to 35	1	30 to 35	3			Paternal aunt	1
35 to 40	1	35 to 40	2			Maternal uncle	1
		40 to 45	1			Paternal uncle	1
						Maternal grandmother	3
						Paternal grandmother	0
						Nephews	2
						Children: Daughter	1
						Son	3

Average Age of Onset	Average Duration of Illness	Average Number of Days of Illness per Month	Heredity positive (21 cases), 87.5%
			Heredity negative (3 cases), 12.5%
17 years	22 years	9½	39 instances in families of 21 patients
			Epilepsy in family history, 0

Report of Clinical Material.—A group of 24 patients suffering from unmistakable migraine have been under observation and have received various forms of treatment for periods varying from a few months to many years. Table 1 contains data as to age distribution, age of onset, duration of illness, severity in terms of days of headache per month and hereditary factors. Table 2 gives the efficacy of various forms of treatments, especially the response to ergotamine tartrate.

Treatment with Vitamin B_1.—From a study of these data and the literature, both recent and remote, and from long experience with migraine problems, the most tenable conclusion seems to be that migraine is a total tissue ailment or toxemia, of which the headache is only the most distressing manifestation. Whether this total disorder (probably allergic) is cumulative and eventually overflows in the form of migraine headache, or whether it represents a static but constant allergic charge which is set off by the alterations in the sympathetic nervous system accompanying emotional stress or nervous tension cannot be positively known at this time. The majority of clues seem to lead to this concept of total tissue toxemia, which interferes with cellular metabolism and disrupts the vasomotor control. Of particular interest in relation to this metabolic concept is the work of Peters (*Lancet* **1**:1161 [May 23] 1936) and others on biochemical disorders

TABLE 2.—*Comparative Value of Methods of Therapy in 24 Cases of Migraine*

Therapy	Cases	Results	Benefit	No Benefit
Oxygen	2	Slight help at beginning of attack; no help after severe attack had begun		
Ergotamine tartrate	17	Hypodermically	(58.8%)	(41.2%)
		Produced or aggravated nausea	1	1
		Produced or aggravated vomiting	6	6
		Produced other toxic manifestations (Abdominal pain and cramps, pain in extremities, precordial pain, severe vertigo)	3	2
		Oral		
		No untoward effects	1	..
		Produced or aggravated nausea	2	8
		Produced or aggravated vomiting	1	4
		Produced other toxic symptoms (Same as above)	1	1
		Temporary benefit, but effectiveness lost	1	..

Therapy	Cases	Results
Allergic diets (Based on cutaneous tests by allergist) (complete tests in 4 other cases revealed no allergy)	7	No response in any way, 4; slight response, but severity of migraine not reduced, 3
Empiric diets	13	No benefit, 6; slight benefit (questionable), 3; definite improvement, 2; temporarily helped, 2
Elimination of wheat, sea food, chocolate, whiskys, eggs, mushrooms and strawberries; low carbohydrate and salt intake, limitation of fluids		
Benzedrine sulfate	3	No benefit
Endocrine therapy	10	Slight benefit in general, 2; no benefit, 8
Thyroid extract, estrogenic substances, adrenal cortex, testosterone, gonadotropic substance		
Autogenous vaccines	2	No benefit
Saline purges	5	Occasional attack aborted
Dilantin	2	No benefit
Psychoanalysis	3	No benefit
Freudian	2	
1 over 5 yr., 1 over 1 yr.		
Adlerian	1	
Analgesics (in order of efficacy)	24	
Morphine (4 cases)		Some temporary help in nearly all cases
Acetylsalicylic acid, acetophenetidin and codeine (gelonida treupel)		Some temporary help in nearly all cases
Empirin compound *		Some temporary help in nearly all cases
Amytal compound		Some temporary help in nearly all cases
Peralga †		Some temporary help in nearly all cases
Aminopyrine		Some temporary help in nearly all cases
Acetylsalicylic acid and bromides		Practically useless in moderately large doses
Acetylsalicylic acid and phenobarbital		Practically useless in moderately large doses
Allonal ‡		Practically useless in moderately large doses
Amytal and acetylsalicylic acid		Practically useless in moderately large doses
Alka seltzer ¶		Practically useless in moderately large doses
Acetylsalicylic acid		Practically useless in moderately large doses
Surgical	5	No benefit
Injection of alcohol in infraorbital and supraorbital nerves	1	
Panhysterectomy	1	
Curettage	1	
Sinus operation	2	

* A proprietary preparation of acetylsalicylic acid.
† Aminopyrine diethylbarbiturate.
‡ Allylisopropylbarbituric acid with aminopyrine.
¶ Acetylsalicylic acid, monocalcium phosphate, sodium bicarbonate and citric acid.

associated with vitamin B_1 deficiency. Peters pointed out that the acute symptoms of vitamin B_1 deficiency are often not sufficiently stressed, although the chronic symptoms of true polyneuritis are generally recognized. He observed that pigeons deprived of vitamin B_1 show rapid development, within twenty-four hours, of symptoms indicating a severe disorder of the nervous system. There is opisthotonos, followed by cart wheel convulsions. Vision is disturbed, and the bird does not respond when a finger is placed before the eye. Exercise, noise or strong light exaggerates the symptoms, whereas rest in a dark, quiet room causes the bird to become quiescent. In the terminal stages of the acute reaction there are failures in regulation of temperature. Peters expressed the belief that the acute symptoms are due to toxic products of vitamin B_1 deficiency, of which the only ones known at present are lactate and pyruvate. Motivated somewhat by the suggestions contained in Peters' work on the biochemistry of vitamin B_1, and largely by the conviction that there exists in patients with migraine a total body toxemia of metabolic origin or the absence of deficiency of an enzyme essential to normal tissue metabolism, I began to make observations on the effect of vitamin B_1 concentrates. For this study a number of patients refractory to all forms of therapy were chosen. No satisfactory results were forthcoming from oral administration alone, but to intramuscular injections of large doses of thiamin chloride the response was surprisingly prompt and gratifying. For a test period of six months the cooperation of 11 patients with severe migraine was obtained. A preliminary report on the results seems worth while, even though the time interval is short and the cases are too few to warrant extensive conclusions.

NOTE.—At the end of one year the results are better established and the incidence of complete relief is about 65 per cent.

Technic of Vitamin B_1 Therapy: In cases of severe migraine daily intramuscular injections of synthetic vitamin B_1 (thiamin chloride) in doses of from 30 mg. to 90 mg. are given for a period of two weeks. The dose can be increased or decreased, depending on the severity of the condition and whether or not treatment is begun during a seizure of migraine. After the second week, 30 mg. is given three times a week for two weeks, and then 30 mg. is given once or twice a week for two months. The dose is increased if attacks of migraine are threatened. If an attack is to be terminated 60 or 120 mg. may be given intramuscularly or intravenously. If given intravenously, the dilution should be 3 cc. of distilled water to each cubic centimeter of the concentrated (30 mg. per cubic centimeter) solution of thiamin chloride. There is little difference between the response to the intramuscular and that to the intravenous method. A capsule containing 10,000 U. S. P. XI units of vitamin A, 200 international units of vitamin B_1, 40 Sherman-Bourquin units of vitamin G (B_2), 500 international units of vitamin C and 1,000 U. S. P. XI units of vitamin D is given three times daily during the entire course of treatment. If a favorable response does not occur within four weeks, liver extract is given intramuscularly in doses of 15 U. S. P. XI units once or twice a week. The total plan of treatment should be continued for three months, whether or not a favorable reaction has occurred.

Results: This report outlines the results for the 11 patients with severe migraine under treatment for approximately six months. The effectiveness of vitamin B^1 therapy in terminating attacks of migraine is illustrated by the fact that of thirty-two attacks of migraine headache, twenty-four (75 per cent) were interrupted within an average time of two and a half to three hours after intramuscular or intravenous injection of from 30 to 90 mg. of vitamin B_1. Two of the thirty-two attacks were partially relieved in that there was recovery from nausea and general feeling of malaise, and in only six attacks (19 per cent) did the headache fail to respond to the first dose of vitamin B_1. The total improvement in the six month period is shown in table 3.

In addition to striking relief from headache, attention is called to the beneficial general effects of the treatment. In almost all instances of headaches occurring in the course of treatment the attacks were of less severity and of shorter duration and were not accompanied by nausea or vomiting. There was not the "poisoned feeling" which usually accompanied or followed the migraine episode before treat-

ment. Other somatic effects were increased appetite, improvement in general appearance, gain in weight, improvement in digestion and elimination and what patients described as general "toning-up." It is fully appreciated that six months is a brief period of treatment even for a preliminary report on the efficacy of any therapy. However, it will be noted that in all the 11 cases reported the migraine was very severe and that all other forms of therapy had failed. One patient, for example, was disabled twenty days in each month; another was unable to hold a position because of the gravity of the illness, and another was so hampered by constantly recurring headache that suicide was often contemplated. When these and other factors are taken into account, the actual ratio of improvement is striking. The average monthly dose of vitamin B_1 was between 350 and 450 mg. In some instances in which response to vitamin B_1 therapy alone was not prompt, liver extract was given by intramuscular injection, as in the method of Borsook (personal communication to the author) for the treatment of trigeminal neuralgia.

TABLE 3.—*Results of Treatment with Vitamin B_1 in 11 Cases of "Severe Migraine"*

Case	Duration of Treatment, Mo.	No. of Days of Headache in Equal Periods: Before Treatment	No. of Days of Headache in Equal Periods: Since Treatment Began	Comment
1	5+	96	15	Gain of 11 lb.; headaches after treatment also less severe and less prolonged
2	5+	50	9	Headaches after treatment markedly diminished in duration and severity; no nausea or vomiting
3	5+	30	2	The two headaches occurring after treatment terminated promptly by intramuscular administration of 60 mg. of vitamin B_1
4	5+	40	5	Constant headache for 5 days while on camping trip in Maine woods; no other headaches during treatment
5	7	102	11	Headaches occurring after treatment also less severe and aborted in every instance by administration of vitamin B_1
6	6	51	3	Headache for 3 days three weeks after stopping treatment; no others in course of treatment
7	6	60	2	Headache occurred 6 weeks after stopping treatment; one other headache only in course of treatment
8	5	48	1	
9	5	90	6	
10	5	46	5	
11	6	68	17	Daily headaches while on ocean cruise, in spite of treatment; "after treatment" headaches reduced in severity and duration

When the migraine episode is divided into three stages, certain features stand out as of particular significance in relation to the toxic manifestations, the vasomotor phenomena and the effectiveness of various therapeutic measures. The following train of events is suggested: (1) the cumulative or premonitory stage (toxemia); (2) the stage of sympathetic imbalance, resulting in cerebral vasodilatation (headache), and (3) the stage of elimination (recovery).

It is in the first phase of the episode that oxygen therapy, purgation, vitamin B_1 therapy and other measures have their greatest effectiveness. Theoretically, these measures have in common an enforced eliminative or detoxifying action, which may remove from the gastrointestinal tract, the liver or the tissues certain toxic (allergic?) agents. The subsequent series of events culminating in the headache may thereby be avoided. In all the cases in which treatment with vitamin B_1 is now under way there appear on the record numerous notes as to "threatened attacks" which were aborted in the preliminary stage. The second stage, of cerebral vasodilation, is not as easily reversible. More heroic measures must be attempted, and the success of any therapy in this phase is, in my experience, somewhat limited. Only 58.8 per cent of the patients studied obtained any relief from ergotamin tartrate, and most of those experienced some form of toxic reaction.

The third, or eliminative, stage is an obvious one. In 20 of 24 cases there was increased output of urine following the headache; in 6 the headache was not terminated until the vomiting had been severe, and in 4 diarrhea followed nearly every attack. In 22 of the 24 cases there was generalized muscular soreness of nearly a day's duration after the headache, and in 19 cases recovery followed a deep sleep of from two to ten hours. It has been noted that a cathartic and diuretic action, and in some cases a period of sleep, followed administration of vitamin B^1 during an attack of migraine.

Summary.—Treatment of migraine up to 1935 had no uniform pattern, except perhaps in the use of analgesic drugs. The clinical use of ergotamine tartrate since that date has proved that drug to be a powerful palliative, successful in the majority of cases. Experience with its toxic reactions of varying severity and its failure to relieve pain in more than 58.8 per cent of our cases has motivated the search for a less toxic, possibly remedial, and more generally helpful substance. Migraine is an illness for which there are many causes, and it is doubtful that any one drug will provide universal relief. Few conclusions as to the efficacy of vitamin B_1 therapy in this experiment are permissible at this early date. Large doses have, however, successfully interrupted severe attacks in a number of cases. Vitamin B_1 seems to have some action in correcting or partially alleviating, or in giving impetus toward a correction of, the cumulative toxic process which leads to the attack of migraine.

DISCUSSION

DR. BERNARD J. ALPERS: I have been particularly interested in the group of patients that Dr. Palmer has under treatment, and I have been able to try the method in a few cases of my own. The group that interested me especially was the one that resisted all forms of therapy, for it is these patients who come to the neurologist for relief. I have had several patients for whom ergotamine tartrate did nothing at all, whether given intramuscularly or intravenously.

I tried Dr. Palmer's method with a patient who was resistant to ergotamine tartrate, with excellent results. This patient had severe headaches at the time of her menses. They were accompanied by depression and other signs. She responded well for at least two periods. This was the first interval of freedom she had had for some time. Her physician persuaded her to discontinue the vitamin B_1 to see what was producing the effect; she is not taking the drug now. Her menses are approaching. She is beginning to feel depressed and has severe headache. This headache, incidentally, was not relieved by large doses of thiamin chloride. I can cite another example in which vitamin B_1 therapy was a real help. I do not understand the rationale of the treatment. I am unable to obtain a clear idea as to the physiologic basis of this therapy. However, it does give temporary relief. This indicates that migraine has many causes, and probably no one method of treatment will help all types of migraine. That seems to be true of ergotamine tartrate. Administration of thiamin chloride may be another effective method of treating migraine, although not effective in every case.

DR. ALFRED GORDON: I have obtained therapeutic benefit from the use of vitamins of various types in the treatment of migraine.

DR. S. B. HADDEN: I have obtained a spectacular result in a case of severe migraine with the use of injections of liver extract, which originally were given not for the migraine but for secondary anemia.

DR. F. H. LEWY: Was the excretion of vitamin B_1 determined before treatment?

DR. A. SPIEGEL: Migraine of many years' duration has been observed to end in thrombosis of the arteries. Dilatation of the vessels can hardly explain such observations. The question arises: Can one discard the old theory of vasoconstriction? I think there is not yet enough evidence for that. The effect of ergotamine tartrate is complicated. It may produce dilatation of the constricted muscles by blocking sympathetic impulses; it may stimulate the vascular wall directly. Another factor in the pathogenesis of migraine may be the effect of toxemia on the brain, producing swelling. It seems not impossible that the effect of vitamin therapy may be due partly to some action on the swelling of the nerve tissue.

DR. J. C. YASKIN: Will Dr. Palmer indicate the severity of the attacks in his cases?

DR. TEMPLE FAY: I wish to ask Dr. Palmer if there has been noted any alteration in blood pressure prior to the seizure and during the attack? If so, has the administration of vitamin B_1 altered that factor in any way?

The use of histamine, intravenously, with its accompanying headache has given rise to the idea that the histamine itself is responsible for the headache. When infusions of histamine are carried out for more than half an hour, the patient fails to experience a headache until the intravenous injections cease. Wolff showed conclusively that the headache was coincident with the returning blood which dilated the vessels. The pressure of the rising blood increased the "stretch" mechanism and precipitated the headache.

Two questions occur to me. If a general toxic factor is to be considered, why should it select just the arterial tree of the head? It is strange that pain is not a phenomenon of other arteries during a "toxic attack." Since I have demonstrated that pain fibers in the brain are observed chiefly on the vessels, I do not think one can overlook the fact that selection of a certain portion of the arterial tree implies another predisposing and unknown factor.

DR. HAROLD D. PALMER: In answer to Dr. Alpers' question regarding my theory, I must confess that I have no conclusive one at the present time. In general, my thoughts have been along the line indicated in the paper, namely, that there is a cumulative toxic state, or possibly a deficiency in tissue enzyme action, which culminates in the migraine episode. I am unable to explain the beneficial effects except on the basis of such a concept. I wish to stress again the experimental nature of the study, and also that this paper represents only a preliminary report. I feel that at least a year of continued use of the treatment in a larger series of cases will be necessary before any definite statements as to a theory are put forth.

I am interested in Dr. Gordon's statements that he finds vitamins of all types helpful. I have thought that oral administration of vitamins A, C and D added something to the vitamin B_1 therapy in my cases. It seems that anything which helps to eliminate metabolic stasis is helpful in treatment of migraine.

Dr. Hadden's report on his success with liver extract in a case of migraine is indeed welcome. Liver extract contains some of the vitamin B complex, and in a communication from Dr. Borsook, at the Pasadena Institute of Technology, I learned that he secured much better results in his treatment of trigeminal neuralgia with vitamin B_1 when he added concentrated solutions of liver extract. After learning of his work, I attempted to increase the efficacy of vitamin B_1 therapy for migraine by the addition of liver extract. However, of 12 patients to whom liver extract was given, 7 had what appears to be a toxic reaction to the intramuscular injections of liver concentrates. Some patients reported a "sickish," bilious feeling; 2 had severe local reactions, with pain and swelling at the site of injection; 1 had mild icterus, and several showed signs of threatened migraine. In a few cases the addition of liver extract has seemed to improve the general response to the treatment.

Dr. Lewy's question about quantitative vitamin B_1 determinations is embarrassing, since, obviously, that should be the first step in a study of vitamin B_1 therapy. A practicable means for quantitative determination was not found, but in recent weeks methods have been studied in order to make such an improvement in this investigation.

With regard to Dr. Spiegel's remarks concerning vascular spasm and vascular dilatation in migraine, I recall Riley's mention of "red" and "white" migraine. The former was considered to be of the angioparalytic or vasodilatory type, and the latter of the angiospastic or vasoconstrictive type. Since Riley's discussion of these points, there has been consideration of vasoconstriction as the preliminary stage in most migrainous reactions and of vasodilatation as the direct cause of the headache stage. Many of my patients have vasoconstriction in the extremities, with cold clammy hands and feet, and yet have marked vasodilatation in the head and face, with flushed cheeks, injection of the conjunctiva, lacrimation and unilateral swelling

of the face and head. It may be that the success which Dr. Weiss has had with dilantin can be explained on the basis of the prevention of this preliminary vasomotor spasm. In other words, if the prodromal stage of vasoconstriction can be overcome, perhaps the subsequent train of events in the migraine episode can be avoided.

Dr. Yaskin asked regarding the severity of the migraine in the 24 cases I have discussed; it is a question which was considered carefully throughout the study. There were 35 cases in the original series and 11 were excluded because the disturbance did not seem to fit into the classic migraine picture. I believe that migraine headache can be of several weeks' duration, and from personal experience I can testify that migraine headaches have lasted as long as three weeks. In my series of patients a week or ten days of continuous headache has not been uncommon.

Dr. McConnell's remarks about "jumping on the vitamin bandwagon" are apropos. In defense of the generous use of vitamin B_1, I may say that, after all, this therapy has been helpful in a number of cases, both in interrupting severe migraine headaches and in preventing the episodes. Furthermore, it is a food substance and not a potent toxic agent, such as ergot, and, as far as can be learned, even doses enormously greater than I have used have not produced any untoward symptoms. In addition, vitamin B_1 is a general tonic, specifically indicated in certain disorders of nutrition and neural involvement. A more innocuous treatment for migraine could hardly be conceived of.

Dr. Fay has brought out what is probably the fundamental problem in his discussion of blood pressure and vasomotor changes. I have had several patients under observation in the hospital and have studied them extensively; included in this study have been observations on the response of the blood pressure to vitamin B_1 therapy. I have found that hypotension has paralleled the stage of fatigue, lassitude and malaise. Intravenous injections of thiamin chloride, in doses of from 60 to 90 mg. have raised the systolic pressure slightly and the diastolic pressure 10 to 20 mm., have increased the pulse rate and have caused slight changes in the electrocardiogram, which have yet to be fully interpreted. Marked diuresis has followed the intravenous and intramuscular injections, and a cathartic action has been reported by a number of patients. Recently, Dr. Donald W. Hastings gave a patient suffering from delirium tremens 50 mg. of vitamin B_1. Before the injection the patient was delirious and maniacal and was obviously suffering from severe cerebral edema. After the intravenous injection he went to sleep quietly, experienced marked diuresis and, after several hours, awakened mentally clear and apparently recovered from the episode. Here is obviously an instance of reduction of cerebral edema by vitamin B_1.

DR. TEMPLE FAY: The experiments to which I referred were those performed by Wolff and his co-workers on physician volunteers. They produced headache of severe character in normal persons by the infusion of histamine.

DR. HAROLD D. PALMER: In my study I administered 0.5 mg. of histamine phosphate to a patient during an acute migraine episode. The result was severe exaggeration of the pain and vomiting. Some authors have stressed the importance of suggestion in the management of patients with migraine, but I have never found it to be of any value. A splendid test of the value of suggestion might be arranged by giving histamine phosphate plus strong suggestion therapy to a patient during an acute migraine seizure. The conclusion, I believe, would be that the suggestion treatment under these circumstances was not particularly valuable.

The question of histamine in relation to headache has been recently discussed by Horton, McLean and Craig, who described a new syndrome of vascular headache and reported (*Proc. Staff Meet., Mayo Clin.* **14**:257, 1939), the results of therapy with small doses of histamine. I have made the histamine test which they recommended in a number of cases of migraine. The results have been negative. With regard to the selection by the migraine process of certain cranial arteries, implying an unknown predisposing factor, I wish to state my belief that the vasomotor changes in migraine represent a fixed, hereditarily predisposed pattern in the sympathetic nervous system, similar in type to the paroxysms of asthma, and involving merely a different system.

Dr. Fay's statement that other arteries are not involved in migraine apparently disregards the very frequent occurrence of the various "migraine equivalents." Abdominal and precordial pain and many other types of migraine equivalent have been extensively reported.

Use of Syntropan in Treatment of Parkinsonism: Preliminary Report.
Dr. Nathan S. Schlezinger and Dr. Bernard J. Alpers.

A clinical evalution of the effectiveness of syntropan (the phosphate of *dl*-tropic acid ester of 2, 2-dimethyl-3-diethylamino-1-propanol) in the treatment of parkinsonism was made in a group of 16 patients. The maximum therapeutic dose was carefully determined and concluded to be 2,400 mg. daily. Of the 13 patients in this series who were potentially capable of reaching this therapeutic dose, there were 3 in whom toxic manifestations were sufficient to prevent effective treatment. In 10 patients symptomatic relief in the form of diminution of salivation, tremor and muscular rigidity was obtained, which essentially equaled that obtained by means of atropine. However, the blurred vision, flushed face and dryness of the mucous membranes, which are regularly associated with atropine or stramonium medication, were conspicuously absent when syntropan was administered in therapeutic doses. From these results it would seem that syntropan is useful in many cases in which atropine cannot be given because of toxic symptoms. Syntropan may also prove to be the remedy of choice in cases of early parkinsonism, in which the by-effects of atropine would be annoying, and possibly incapacitating.

DISCUSSION

Dr. Paul Sloane: The use of syntropan is advocated in the treatment of parkinsonism because, as far as I can see, the toxic symptoms are different from those following other drugs of the belladonna series. However, I noticed that only 4 patients for whom the treatment was effective were without toxic symptoms and 6 showed severe toxic symptoms, although the dryness of the throat and the blurring of vision were not as troublesome as when other drugs were used. A disadvantage of the use of syntropan is the expense, since it is a proprietary drug.

Dr. Bernard J. Alpers: It must be understood that many of these patients were refractory to treatment, as many patients with parkinsonism are. As Dr. Schlezinger has pointed out, atropine is the drug most effective in therapy. In a high percentage of cases my experience did not coincide with that of Dr. Sloane. I find that atropine must be stopped short even of the optimum dose, as can be seen in a few cases in which toxic effects were produced. The dose of syntropan was a maximum one. Dr. Schlezinger failed, I think, to make clear the fact that there is an optimum dose of syntropan. If one exceeds this, one has the same experience as with atropine, namely, evidences of toxicity.

If the optimum rather than the maximum dose of syntropan is maintained, good effects are realized without toxic symptoms.

In the last 3 cases, some of the effects were striking. One case was that of a woman who had had all sorts of treatment. When she consulted me she was completely demoralized, so, more in desperation than anything else, I gave her syntropan. She now is much less depressed. She feels hopeful about herself. She is able to walk without support.

In another case a man had had good effects from atropine—in fact, the best results he had had from any drug. However, he had signs of prostatic obstruction, and when what approximated a maximum dose was reached there developed difficulty with urination. He was disappointed to have to discontinue atropine. It was the only remedy that gave him any benefit. Syntropan was given in a dose of 2,400 mg. a day, and he has had no trouble with his bladder. He has exactly the same result as with atropine, without ill effects.

Another word with regard to treatment with syntropan: I think that a patient who has had no other treatment has better chances of beneficial effects from syntropan.

DR. J. W. MCCONNELL: I wish to ask Dr. Schlezinger whether the disease in all these cases was the so-called postencephalitic form of parkinsonism, or in some was it of the arteriosclerotic type?

DR. NATHAN S. SCHLEZINGER: Dr. Alpers has explained a certain misconception, which resulted possibly through my hasty presentation of the material. The toxic manifestations were deliberately determined in most of the cases; in 5 instances the dose was raised to 3,200 mg. daily.

With administration of from 2,400 to 3,200 mg. daily, no further evidence of improvement was obtained; there were only the toxic manifestations. It is concluded that the maximum therapeutic dose of syntropan for parkinsonism is 2,400 mg. daily. Although 2 of the patients had toxic manifestations, nausea and vomiting, with small doses, no alarming symptoms were obtained with therapeutic doses. The improvement obtained with the dose of 2,400 mg. was not associated with toxic symptoms.

In answer to the other questions: The protocols were not presented this evening; hence, the individual manifestations could not be given in detail. Not only ability to walk but also speech, tremor and rigidity were improved in the patients to a varying degree.

In answer to Dr. McConnell: One patient in the series was considered to have idiopathic paralysis agitans. As to the greater cost of syntropan, that has to be considered, as it must in all forms of therapy for diseases. Many patients are possibly not receiving the maximum benefit from treatment of many other disorders because of their inability to pay the price of the drug. I emphasize that certain patients who can afford to buy syntropan and who might be incapacitated by the blurring of vision due to atropine can be helped by syntropan, and perhaps continue with work for which their eyes are essential.

Decerebrate Tonic Extensor Convulsions as a Sign of Occlusion of the Basilar Artery: Case Report with Autopsy. DR. MICHAEL SCOTT and DR. H. C. LENNON.

This article will appear in a later issue of the ARCHIVES.

CHICAGO NEUROLOGICAL SOCIETY

RICHARD B. RICHTER, M.D., *President, in the Chair*

Regular Meeting, Dec. 21, 1939

Neuromyelitis Optica: Report of a Case. DR. WALTER G. HAYNES.

Neuromyelitis optica, or Devic's disease, as originally described by Devic (*Bull. méd.* **8**:1033 [Nov.] 1894), after assembling the few cases previously reported, is a syndrome consisting of bilateral changes in the optic disks and myelitis involving the low cervical or high dorsal region of the cord. This case is presented to influence opinion as to the right of the syndrome to autonomy; the condition was a clearcut clinical entity which conformed to the syndrome established by Devic and later described in more detail by Michaux (La neuro-myélite optique aiguë, Paris, Librairie Louis Arnette, 1930), Merkel (Ueber einen Fall sogenannter Neuromyelitis optica, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **129**:591, 1930) and others.

REPORT OF A CASE

History.—A white woman aged 24 had been well until one year before admission when she began to experience pain in the upper dorsal region of the back, as high as the level of the scapulas, which sometimes would shoot anteriorly as a girdle pain. It varied from a dull ache to a sharp, stabbing sensation. In

June 1939 the pain increased in frequency and severity, particularly on movement of the vertebral column. In July there developed a feeling of numbness in the right leg, which rapidly involved the left leg and was associated with aching pains in the calves of both legs. The numbness traveled rapidly up to the level of the breasts, so that the patient had no sensation below this line. As the numbness extended the pain in the legs decreased, but the pain in the upper dorsal region continued. For three weeks before admission she had been unable to move her lower extremities, and for two weeks she had had both rectal and vesical incontinence. Vision had begun to blur in June, at the height of the pain and just previous to the advent of the ascending anesthesia. This was not accompanied by pain in the eyes. For a month prior to admission she had been able to distinguish only light from dark with the left eye.

Examination.—The patient presented marked spastic paraplegia, with the following ocular changes: The left eye possessed only light perception; the right had marked constriction of the visual field, with a temporal defect. Fundoscopic examination revealed bilateral primary atrophy of the optic nerve.

There were a Horner sign on the left and a level of anesthesia sharply limited to the second dorsal segment of the cord. Below this there was complete loss of sensations of pain and temperature, light touch and vibration. There was preservation of a very small perianal area of pain and temperature sensibility. The legs were markedly spastic and incapable of motion. The abdominal reflexes were absent; the knee and ankle jerks were markedly exaggerated, with patellar and ankle clonus; the pathologic reflexes of Babinski, Chaddock, Oppenheim, Gordon, Rossolimo and Mendel were present bilaterally.

The blood and urine were normal. Chemical tests of the blood and spinal fluid gave normal results except for the colloidal gold curve, which was 1112332211. Roentgenograms of the skull, the sella turcica and the dorsal portion of the spine all revealed nothing abnormal.

Diagnosis and Course.—The case was diagnosed as one of Devic's disease, and the patient was given large doses of vitamin B_1 intramuscularly and quinine hydrochloride. She made a spectacular recovery and at present has control of her bladder. Sight has improved considerably, and there is anesthesia only below the knees.

Comment.—Recovery is not unusual, there being a mortality rate of 40 to 50 per cent; the disease is self limited, so that patients who survive have partial to complete remission of symptoms. Pathologic differentiation of the disease from multiple sclerosis and disseminated encephalomyelitis has been made previously, notably by Hassin (Neuroptic Myelitis Versus Multiple Sclerosis: Pathologic Study, ARCH. NEUROL. & PSYCHIAT. **37**:1083 [May] 1937), who observed that the gray and white matter were both involved. The nerve fibers, the ganglion cells of the anterior and posterior horns and the axis-cylinders were affected, as were the myelin sheaths. Hassin also found that while the main lesion was in the cervical or dorsal region of the cord, the entire cord was affected, even when there were no plaques, there being swelling of ganglion cells and proliferation of microglia in the sacral segments. The reactive cells were microglia elements rather than astrocytes, as in multiple sclerosis.

Clinical differential diagnosis is not difficult. It is based on the characteristic combination of bilateral optic neuritis and the dramatic transverse lesion of the cervical or dorsal portion of the cord, resulting in spastic paraplegia and complete anesthesia, accompanied by pain. The disease is found in either males or females between the ages of 10 and 60. Multiple sclerosis is rarely associated with bilateral optic neuritis and never with myelitis, according to Russell Brain (Diseases of the Nervous System, New York, Oxford University Press, 1933, pages 397-399). Multiple sclerosis is notorious for its relapses after remission; Devic's disease is self limited, with no relapses. Devic's disease never presents nystagmus, intention tremor or scanning speech, and it usually causes pain, which is rare in multiple sclerosis. Multiple sclerosis only occasionally is associated with severe rectal and vesical disturbances, and it does not exhibit complete anes-

thesia below a sharply defined level. Disseminated encephalomyelitis usually complicates an infection; the numbness does not stop at a definite upper level, and there are usually well defined mental symptoms. There are ataxia and incoordination, and the visual pathways are not involved.

DISCUSSION

DR. G. B. HASSIN.: Devic's disease, or neuroptic myelitis, should be considered as a definite morbid entity, regardless of the fact that signs of disease of the spinal cord combined with blindness may occur in other diseases of the central nervous system (multiple sclerosis, disseminated encephalomyelitis, syphilis of the nervous system and multiple tumors). However, in such conditions there may be additional abnormal clinical manifestations, such as involvement of other cranial nerves, while in neuroptic myelitis the clinical features are confined to symptoms of lesions in the visual system of nerve fibers and in the spinal cord. The same is true of the anatomic changes, which are present only in the spinal cord and in the visual nerve tracts. Grossly, the lesion in the spinal cord in neuroptic myelitis much resembles that in multiple sclerosis because of the presence of patches of demyelination. The difference is that in neuroptic myelitis the ganglion cells are also affected; the patches consist not of a glial scar, as in multiple sclerosis, but of broken-up glia tissue, the cells of which may assume the ameboid character and exhibit features of clasmatodendrosis. In brief, the glia exhibits progressive changes in multiple sclerosis and regressive changes in neuroptic myelitis. An additional noteworthy fact is degeneration of the visual system of fibers—from the optic nerve tract to the occipital pole, where a focus of softening in the calcarine fissure can be seen. The selective involvement of the visual system of fibers may be due to a specific toxic-infectious agent, which should be looked for in every case. Was there a history of an infection or intoxication in Dr. Haynes's case?

DR. JOSEPH A. LUHAN: My interest in this condition was aroused by the observation of a case in which I have made repeated neurologic examinations during the past two years. The onset had been subacute, with disturbance of vision and a modified Brown-Séquard syndrome indicative of a lesion of the fifth thoracic segment, which progressed to the picture of retrobulbar neuritis and a transverse lesion of the thoracic portion of the cord. In spite of this near transection of the cord, there have been well marked variations in the sensory innervation and motor paralysis below the level of the transverse lesion. Apropos of what Dr. Hassin said about the tendency of the disease process to involve the gray as well as the white matter, this patient subsequently had amyotrophy of the distal part of one upper extremity. He represents not the group progressing to recovery, but the 50 per cent, perhaps, who do not recover.

With respect to the absence of cerebral involvement, however, I have observed cases at the Cook County Hospital in which there was evidence to dispute such an assumption. One, particularly, in Dr. Gonda's service, was that of a girl with visual disturbance, blurring of one disk and pallor of the other, transverse myelitis and evidence of involvement of the brain revealed by paraphasia. The patient recovered sufficiently to be able to walk out of the hospital when she was discharged recently.

I was struck with the absence of nystagmus in these cases. It is an important differentiating factor.

DR. WALTER G. HAYNES: In reply to Dr. Hassin's question: We were unable to demonstrate any foci of infection in this case.

Abscess of the Brain of Seven Years' Duration. DR. F. E. POLMETEER, DR. ADRIEN H. P. VERBRUGGHEN and DR. J. K. HANSON, Moline, Ill.

The following case is of particular interest from the standpoint of the difficulties that may be encountered in the diagnosis of organic diseases of the brain.

REPORT OF A CASE

History.—R. M., a boy aged 13 years, who was admitted to the neurosurgical department of the Presbyterian Hospital on July 18, 1938, had been referred by one of us (J. K. H.) with the diagnosis of "brain tumor." The patient complained of numbness and tingling of the left hand, forearm, arm, leg and thigh, which had been present for two and a half years. During the past year there had been headaches, nausea and vomiting, and dizziness, associated with staggering and a tendency to fall to the left. The right eye had become more prominent during the past year; the patient had had difficulty with near vision for the past two and a half years.

In January 1931, at the age of 5, the patient had had a streptococcic infection of the upper lip, which extended upward to the eyes. At this time he lost control of the movements of the eyes and of the lids. There was some localization of the infection to the outer portion of the right orbit, which was incised and drained. The movements of the right eye returned, but those of the left did not. The left eye turned inward and remained so until it was operated on in July 1935. At this time, the left external rectus muscle was shortened, in an attempt to correct the left internal squint and preserve vision in this eye.

The patient was normal in all respects until July 1937, when he began to have severe frontal headaches, associated with nausea, projectile vomiting and photophobia. The right eye was more prominent than the left, and became progressively more so until the date of admission.

The patient continued to go to school and had done average work. In May 1938 there was blurring of vision with pronounced photophobia.

Examination.—The patient was fairly well developed, but emaciated; he lay quietly in bed and apparently was not acutely ill. General physical examination gave normal results except for the presence of dilated veins in the right frontal and parietal regions of the scalp and over the right upper eyelid. The right eye was more prominent than the left.

Neurologic examination revealed that the right pupil was dilated and reacted poorly to light; it measured 6 mm., and the left pupil, 3 mm. There was paralysis of the left external rectus muscle. Ophthalmoscopic examination revealed bilateral choking of the disks of 3 to 4 D. on the right and of 2 to 3 D. on the left. Several hemorrhages were present on the disks and around their margins. The fields appeared normal in rough tests. Reflexes were increased on the left side of the body. There was neither ankle nor patellar clonus, but an equivocal Babinski sign persisted on the left. Sensation was normal throughout. With the maximum designated as plus 4, there were: ataxia, 1 plus, in the left finger to nose and left heel to knee tests, and weakness of the left arm and left leg, 1 to 2 plus. A Romberg sign was present, the patient falling to the left with the eyes closed. He also fell to the left when walking a straight line.

The blood picture was normal, except for a white cell count of 18,500, with predominance of polymorphonuclear cells. The urine was normal.

Anteroposterior and lateral roentgenograms of the skull showed destruction of the floor of the sella turcica and the right posterior clinoid process; all the suture lines were wide open—the usual finding in cases of increased intracranial pressure.

Ventriculographic examination was performed on July 22. At operation, a small amount of fluid was obtained from the posterior horn of the right lateral ventricle. On the left, however, the fluid was under high pressure. By our usual method, 10 cc. of fluid was withdrawn and replaced with a corresponding amount of air, until 60 cc. of air had been introduced into the left lateral ventricle. The ventriculograms showed that the anterior horn and body of the right lateral ventricle were displaced downward and posteriorly and that the entire ventricular system was pushed toward the left. These roentgenologic findings indicated a space-occupying lesion in the right frontal lobe.

Diagnosis.—In view of the slowly progressive history of nausea and vomiting and choked disks, together with the presence of signs on the left side and the absence of sensory disturbances, an expanding lesion of the right frontal lobe,

involving particularly the precentral area, was postulated and confirmed by ventriculographic study. Hence, the preoperative diagnosis was tumor, astrocytoma, of the right frontal lobe.

Operation.—With the patient under anesthesia, induced with avertin with amylene hydrate, a right frontoparietal flap was turned. The dura was tense and nonpulsating. A fluctuant area was felt in the anterior portion of the right frontal lobe. Closer inspection revealed that the bone overlying this area was eroded and that osteogenesis had previously taken place, giving this portion of the bone a roughened, elevated appearance. A small nick was made in the dura and a brain trocar introduced into this soft, fluctuant region. At a depth of 3.5 cm. elastic resistance was encountered, which gave way to slight pressure. The trocar fell into a cavity, and on removal of the stilet thick, odorless, grayish green pus was obtained. Cultures and a smear revealed Staphylococcus aureus haemolyticus. The dura around the trocar opening was coagulated in a circular manner to about the size of a quarter. A small rubber tube was introduced into the abscess and about 80 cc. of pus obtained. The portion of the bone flap immediately overlying the drain was rongeured away and a longitudinal incision made in the skin to accommodate the rubber drainage tube, which was fixed to the scalp by a small suture. Iodoform gauze was laid in place around the drain, and the skin flap was closed with interrupted silkworm gut sutures. The patient's condition was good throughout the operative procedure.

Postoperative Diagnosis.—The diagnosis was abscess of the right frontal lobe of the brain, due to Staph. aureus haemolyticus.

Course.—After the operation the patient was placed flat on his abdomen, with the right side of the forehead down, and the foot of the bed was elevated. Fluids were forced to 3,000 cc. per day, in a further attempt to press the brain against the dura. The wound drained profusely; by the eighth postoperative day there was an infection beneath the entire skin flap. Through and through drainage was instituted, and the wound was irrigated twice daily with mercury bichloride (1:3,000 solution) followed by hydrogen peroxide. Repeated small transfusions of blood were given on the eleventh, twelfth and thirteenth postoperative days. At this time, however, there was difficulty with near vision. The wound continued to drain, and a bacteriophage specific for the invading organism was used to irrigate the wound and dressings twice daily, after irrigation with hydrogen peroxide. A silver nitrate stick was used daily after the thirteenth postoperative day to remove granulation tissue around the rubber drain. The iodoform gauze was shortened at alternate dressings, and on the sixteenth postoperative day it had been completely removed. With this treatment the wound looked clean on the twenty-second postoperative day.

On the twenty-sixth postoperative day adhesive strapping was applied to approximate the margins of the wound at the site of the granulation tissue. Thirty-one days after operation irrigation with bacteriophage was discontinued. The wound had healed well; sutures were removed, and the only complication was a small infected herniation of the brain, measuring 1 by 2 cm. White cell counts from time to time showed a steady decrease from 18,500 to 8,400.

Thirty-four days after operation both fundi showed choking of from 1 to 2 D. There was also difficulty with vision. The granulation tissue continued to fill in the margins of the wound slowly, and in spite of the adhesive strapping and daily applications of a lead plate, the cortex continued to herniate.

On September 10, sixty days after operation, cerebrospinal fluid escaped from the herniation. The rectal temperature rapidly rose to 102 F.; the neck was rigid; there was a bilateral Kernig sign, and cerebrospinal fluid saturated the dressings. Petrolatum gauze was applied to the wound, which was not dressed more frequently than was necessary; fluids were forced, and the foot of the bed was elevated. Drowsiness was produced by administration of elixir of phenobarbital, 1½ grains (0.097 Gm.), every four hours. Under this management, an attempt was made to allow gradual closure of what was regarded as a perforated ventricle. The patient steadily improved; the neck became less stiff; the Kernig sign disappeared on both sides, and the temperature dropped to normal in two days.

On September 19, when the wound was dressed, it was found that the opening into the ventricle had closed. A few days later the patient was discharged, with instructions to return in one month. Ophthalmoscopic examination on discharge revealed bilateral papilledema of only 1 D. Although the patient's vision was still poor, no optic atrophy was observed. The other neurologic signs had disappeared.

While at home, the patient remained in bed, with restriction of activity, for six weeks, the wound being dressed as infrequently as possible. Four months after operation the wound had completely closed and the patient was up and about, but vision was impaired.

In the first part of February 1939, the patient moved from Moline. His general physical condition at that time was normal, and he had gained about thirty pounds (13.6 Kg.) in weight. Vision was only fair, and for the first time early bilateral secondary optic atrophy was said to be observed.

Comment.—In this case it was especially difficult to make a correct preoperative diagnosis because of the prolonged quiescent stage, there being a latent period of seven years from the time of the initial infection of the upper lip. This incident had even been forgotten by the mother and was recalled (postoperatively) only after careful questioning. Without a suitable history of the initial infection the differential diagnosis of an abscess and a cerebral neoplasm is difficult, and in this instance was completely missed. The high leukocyte count and the slight fever were the only suggestive points. Dr. Adson and Dr. Craig (*Ann. Surg.* **101**:7, 1935), of the Mayo Clinic, stated: "If it were not for the history of the infection and the symptoms of the initial stage, it would often be difficult to distinguish those symptoms due to abscess from those produced by a cerebral neoplasm." They also pointed out that in 5 instances they encountered cerebral abscesses when a history of infection was lacking and the patient was operated on for a condition diagnosed as cerebral neoplasm.

Of the solutions used for irrigation beneath the scalp flap in this case, the most striking results were obtained with a bacteriophage which was found to be lytic for the particular strain of staphlococcus as tested in vitro. After its use twice daily for five days, the infection beneath the flap had almost completely subsided. It must be emphasized that at no time was the cavity of the abscess irrigated. The possibility of disseminating the infection, with resulting fulminating encephalitis or meningoencephalitis, is too great to warrant the most careful and skilled irrigation. Such a procedure is to be condemned as dangerous.

Leakage of cerebrospinal fluid in association with drainage of a cerebral abscess is a grave situation, which, as Dr. Bucy (*Ann. Surg.* **108**:961, 1938) pointed out, is often illogically treated because many surgeons fear it. In his series of 17 cases of abscess of the brain, he observed this complication without fatal termination in 6 instances. Of 24 cases of abscess of the brain treated by one of us (A. V.), this is the third in which it has occurred. We are frankly afraid of it and try to avoid it. Although the onset of leakage of cerebrospinal fluid in cases in which a cerebral abscess is draining makes the prognosis less favorable, it does not indicate a fatal termination. Composure, clear thinking and knowledge of the pathologic process are essential. In this case, in spite of our treatment, meningitis developed, and the situation was discouraging. The same rigid rules in force before the onset of the meningitis were followed implicitly. There were no spinal punctures; fluids were forced; the foot of the bed was kept elevated, and the patient was quieted with suitable doses of phenobarbital. With this management the temperature gradually fell to normal on the third day of the infection; the Kernig sign and the rigidity of the neck disappeared.

The escape of cerebrospinal fluid from a perforated ventricle following the drainage of an abscess of the brain is uncommon; moreover, it is not usual for such a complication to terminate favorably. The spinal fluid did not seep up around the brain tissue, but escaped in a constant pulsating stream from a fine opening in the center of the small piece of herniated brain. For this reason we stated that the fluid was derived from a perforation in the ventricular wall, which was drawn up by the collapsing abscess. No doubt in this instance careful management, with certain well defined principles, militated in our favor.

DISCUSSION

DR. ADRIEN VERBRUGGHEN: Perhaps if we had been guided more by the white cell count of 18,000 and less by the history, we might have suspected the presence of this abscess, but there was no evidence in the history. After the pressure was relieved, the ocular condition changed remarkably for the worse. The patient was much less able to see than when the pressure was present. I have had the same experience in a case of medulloblastoma and in another of spongioblastoma. I wonder if any others of the members have noted this change in vision after decompression.

Physiologic Changes in Cerebral Concussion. DR. W. W. SCOTT.

Teratoma of the Spinal Cord: Report of a Case in Which the Origin Was Tridermal. DR. MABEL G. MASTEN, Madison, Wis.

A case of tumor of the spinal cord at the level of the sixth cervical segment in a girl aged 5 years is reported. The clinical features indicated a short duration of symptoms, with pain and rapidly developing paralysis predominating. The latter became more complete after a lumbar puncture, which was complicated by symptoms of spinal shock.

At operation, a cystic tumor containing mucus was observed attached to the pia by a short pedicle. The cyst was lined by a variety of epithelium, from low cuboidal to pseudostratified. The solid portion of the tumor showed a complex structure, and the following tissues and cells were identified: peripheral nerves and ganglia; nerve cells; a cavity resembling the central canal, lined with ependymal cells and surrounded by glial tissue; pacinian corpuscles; adipose tissue; collagenous connective tissue; smooth muscle; striated muscle; cartilage; bone; mucous glands, and squamous, cuboidal, pseudostratified and ciliated columnar epithelium. The orderly arrangement of ciliated epithelium, mucous glands, ducts, cartilage and smooth muscle suggested the anlage of the respiratory tract, and it was concluded that the tumor was derived from all three germ layers.

DISCUSSION

DR. A. EARL WALKER: I saw the patient whose case was previously noted by Bucy and Buchanan (*Surg., Gynec. & Obst.* **60**:1137 [June] 1935). The specimen histologically was similar to the one reported on this evening. Clinically, however, because the tumor was lower in the spinal canal the symptoms were different. The complaints were pain in the legs and weakness of the left leg. There were no sensory changes, the neurologic disturbances being entirely motor and reflex and confined to the legs.

The spinal canal at the site of the tumor was markedly dilated. The pedicles were thinned, and the canal was practically twice the normal width in the lower thoracic and the upper lumbar region. I wonder if the roentgenologic changes were similar in the present case.

The patient, now 8 years old, returned for observation on Dec. 12, 1939. He made no complaints whatever. Except for absence of knee and ankle jerks, no abnormalities were found on neurologic examination.

Association of Homonymous Hemianopia and Unilateral Absence of Alpha Waves. DR. THEODORE J. CASE.

In March 1938, absence of or marked difference in the alpha waves on the two sides of the brain was discussed before this society as a criterion in the diagnosis of intracranial tumors (Localization of Cerebral Cortical Lesions by Electroencephalographic Examination, ARCH. NEUROL. & PSYCHIAT. **40**:623 [Sept.] 1938). Since, 8 cases have been seen in which this absence of or difference in the alpha waves was present; in all homonymous hemianopia was noted.

Operations in 5 of the 8 cases have revealed the approximate position of the lesion. In 2 of them there was a tumor of the temporal lobe, in 1 a traumatic

cyst of the temporal lobe, in 1 a tumor of the occipital lobe and in 1 an intraventricular tumor which involved the optic radiations.

The common features of the 5 cases were involvement of the optic radiations and homonymous hemianopia. These cases suggest that the alpha waves may be a cyclic electrical phenomenon circulating in a chain of neurons, one link of which is the optic radiations. Unilateral loss of occipital alpha waves is associated with homonymous hemianopia, both probably resulting from destruction of the optic radiations.

Unilateral loss of the occipital alpha waves or a gross difference in the size of these waves on the two sides constitutes a sign of signal importance in the diagnosis of lesions of the temporal and occipital lobes.

RICHARD B. RICHTER, M.D., *President, in the Chair*

Regular Meeting, Jan. 18, 1940

Surgical Treatment of Unilateral Choreoathetosis. DR. PAUL C. BUCY.

E. S., aged 21, was injured in an automobile accident in October 1935; he received a severe injury to his brain and is said to have been unconscious for twenty-eight days. In January 1936 there began uncontrollable, involuntary movements of the left arm and leg. Gradually the movements in the leg disappeared but those in the arm continued unchanged. These movements disappeared only when he was asleep or under the influence of a large quantity of alcohol. The effect of large quantities of alcohol on the movements were confirmed by observations in the hospital.

On Dec. 9, 1939, the right precentral arm area was extirpated. After the operation the involuntary movements were completely abolished and have remained so to date. Gradually, in the five and a half weeks which have elapsed since the operation, the patient has recovered considerable voluntary movement of the left upper extremity; movement at all joints is possible, although fine, well coordinated movements of the hand and fingers are not possible and the patient cannot move any one finger without moving all the others simultaneously.

Motion pictures of the preoperative state are shown, and the patient himself is presented to demonstrate his present condition.

DISCUSSION

DR. ERIC OLDBERG: I am much interested in this work and have had experience in cases of this type through a different approach—section of the extrapyramidal tract. This method has some advantages over the cortical extirpation which Dr. Bucy described. There is no increase in weakness, and the immediate cessation of the movements is spectacular. However, the disadvantage, which I think cortical extirpation does not have, is that in my opinion extrapyramidal sections do not produce permanent results. In from three to six months some of the involuntary movements recur and in a year or two they may be nearly as severe as before operation. In 1 case, in which I sectioned the extrapyramidal tract for relief of violent movements, the trouble returned in a year and a half in nearly the same intensity. I referred the patient to Dr. Bucy, who performed cortical extirpation. I do not know what the results of the last operation are, but I am inclined to believe they will be better.

DR. LLOYD H. ZIEGLER: The movements shown in this case are not what I have been accustomed to call those of athetosis. They resemble somewhat the hammering movements seen in the clinical syndrome of hemiballismus, in which the body of Luys of the opposite side is implicated.

DR. PAUL C. BUCY: I wish to say, first, that this operation was performed only six weeks ago, and I am sure Dr. Oldberg will agree that no one can judge the result in that time. I am showing this patient not as illustrating a final result but because he lives at a distance and is leaving tomorrow.

I am not ready to give a final answer as to results of this or any other surgical procedure designed to relieve involuntary movements. At present, the indication is for each surgeon to continue with the procedure which he prefers, to improve and modify it as is indicated and to make careful detailed observations. In the course of a few years one will probably arrive at some opinion as to which procedure is best.

Dr. Ziegler has touched on one of the difficult phases of this problem, the terminology. Apart from the more or less typical, and usually easily classifiable, involuntary movements, such as the intention tremor characteristic of destruction of the dentatorubrothalamic pathway, the tremor of parkinsonism during rest and the movements seen in Sydenham's and Huntington's chorea, there are a large number of different movements which are difficult to classify. It is even more difficult to present an accurate word picture of them by any brief term. For that reason I have shown the motion pictures in this case. To these various involuntary movements, which are not rhythmic, and which do not reproduce exactly the same movement over and over again, I have not hesitated to apply the term choreoathetosis, even though it is by no means accurately descriptive. Unfortunately, such terms as hemiballismus and acute hemichorea do not provide the hearer with any more accurate picture of the movements which are present.

I do not believe that one can with certainty conclude that the fundamental lesion in this case lies in the corpus Luysi. I do not know where it lies, but I am convinced from the pneumoencephalograms that there is atrophy of the right thalamus, and possibly of the right basal ganglia.

Relationship of Orthostatic Hypotension to Myasthenia Gravis. DR. ALEXANDER R. MACLEAN, Rochester, Minn.

The syndrome of orthostatic hypotension is described, and 3 cases of definite orthostatic hypotension are presented. The patients had been treated with prostigmine and guanidine hydrochloride. The prostigmine and guanidine hydrochloride produced a marked effect on the abnormal orthostatic blood pressure of these patients. The improvement in the blood pressure was maintained over considerable periods.

Two other cases of orthostatic tachycardia are presented in which a similar improvement was exhibited with guanidine and prostigmine medication.

Three other cases of orthostatic tachycardia are described in which no response to prostigmine and guanidine medication was shown.

There appears to be a definite relation between myasthenia gravis and typical orthostatic hypotension in that both respond to the same types of therapy; ephedrine, prostigmine and guanidine.

DISCUSSION

DR. ERIC OLDBERG: Were any of these studies made on patients with narcolepsy or with early manifestations of amyotrophic lateral sclerosis?

DR. VICTOR E. GONDA: I wish to ask Dr. MacLean how he made the diagnosis of myasthenia gravis. From the clinical symptoms? Or did he study a biopsy specimen of muscle microscopically? Did he find electric changes corresponding with those of Jolly? Did he determine the sugar content of the blood before and after the fall of blood pressure?

DR. LLOYD H. ZIEGLER: Did Dr. MacLean's patients use tobacco to excess? Dr. Walter Cannon, in his book entitled "The Wisdom of the Body," reported changes in the blood serum in hypotensive states related to shock. Were such changes observed in Dr. MacLean's patients? The phenomena of hypertension and hypotension are interesting and may be related in some unusual way. Dr. MacLean may be getting close to this relationship.

DR. BENJAMIN BOSHES: Were any studies made on the creatine content of the urine? In view of the fact that patients with myasthenia gravis may show increased excretion of creatine, this determination might be a valuable differentiating point between myasthenia gravis and simulating conditions.

DR. ALEXANDER R. MACLEAN, Rochester, Minn.: In answer to Dr. Oldberg: I have seen orthostatic hypotension in cases of neurosyphilis and amyotrophic laterial sclerosis. In no instance have I given prostigmine.

The dose of the guanidine hydrochloride was from 0.5 to 0.75 Gm. With this dose the patients occasionally complained of annoying paresthesia of the hands and face.

In reply to Dr. Gonda: In the first case of orthostatic hypotension presented this evening, the typical myasthenic fatigue reaction of the striate muscles was demonstrated on electrical stimulation. However, I have hesitated to accept this as proof of a myasthenic entity. I have not studied any of the interesting problems concerning which Dr. Gonda has asked because, as I mentioned in my initial sentence, this work represents merely the beginning of a study which I hope to complete later.

Spinal Dysraphism: Spina Bifida and Myelodysplasia. DR. BEN W. LICHTENSTEIN.

This paper will appear in a future issue of the ARCHIVES.

Neuropsychiatric Complications Following Severe Loss of Blood. DR. NORMAN REIDER.

This paper will appear in a future issue of the ARCHIVES.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

R. GORDON BRAIN, M.D., *President, in the Chair*

Regular Meeting, Jan. 11, 1940

Results of Therapy in Cases of Sexual Deviation. DR. LOWELL S. SELLING, Detroit.

The problem of treating sex offenders is important. There has been some feeling that such offenders cannot be treated successfully, but the present study indicates that a certain percentage can be helped by various procedures. Treatment is modified by such considerations as feeblemindedness and senility and by the psychiatric mechanisms involved. Glandular treatment has not been used enough to indicate what success will be achieved. Surgical treatment apparently is contraindicated. Psychiatric treatment consists of: (1) release therapy, in which the patient can talk out his complex material; (2) recreational therapy, in which recreation is substituted for daydreaming and abnormal sexual practices; (3) adjustment of marital relationships, and (4) individual advisory treatment, in which the patient is advised as to conduct and is guided through a probationary period. Suggestion therapy has proved to be of value. Psychoanalysis and hypnosis have not been tried in the psychopathic clinic, but the literature indicates that they serve a purpose. The various laws in Michigan relating to sex are summarized.

DISCUSSION

DR. MILTON H. ERICKSON, Eloise, Mich.: I am pleased with the emphasis Dr. Selling has placed on the psychiatric aspects of the problem. Although there

has long been a limited realization that the person displaying sexual deviations constitutes a psychiatric problem, its public recognition and its acceptance by psychiatrists in general have been only recent, and have been made possible by the well publicized sexual crimes of persons obviously committable to a hospital for mental disease or with a history of previous commitments. In discussing the possibilities of treatment, Dr. Selling has stressed the importance of the classification of sexual offenders in relation not only to the type of deviation but also to such important considerations as constitutional endowments and status and psychologic forces and motivations. In the past, this need was neglected with, instead, acceptance of a formal legalistic classification, which took cognizance of the offense and not of the offender. However, I wish Dr. Selling had given more detailed information as to a desirable systematic classification, since this is a matter on which all need information before the problem can be dealt with adequately.

My own tendency is to classify sex offenders according to three categories, these categories being determined by the underlying causes and factors as well as by the therapeutic possibilities. 1. Sexual offenders whose deviations and aberrations derive from organic changes, such as those which accompany senility, arteriosclerosis, alcoholic deterioration and disease of the endocrine glands. Treatment of offenders of this type is essentially medical and surgical, and is directed primarily to conditions other than the sexual deviation, the latter being often only an accidental or incidental manifestation and at most of only secondary consideration. Prognosis for this type of sexual offenders depends primarily on the organic condition.

2. Persons with a type of sexual deviation that derives from the little understood and inexplicable factor best termed, with present lack of understanding, "constitutional endowment." It is a sexual offender of this type who, despite every effort to understand him and every measure of treatment that seems suitable, remains an offender, and hence gives force to the idea that he was born that way and will remain so despite every effort made to correct his difficulties. It is in this group that one places the confirmed homosexual person, the exhibitionist, the voyeur and the fetishist, who appear to be utterly incapable of reaching an adult heterosexual development; the deviation seems to be an essential part of the total personality. Treatment for this class is essentially a matter of hospitalization until psychiatric progress provides an adequate means of meeting the problem. At present these are the offenders who arouse such punitive attitudes on the part of society, which in turn have led both to drastic attitudes and unsatisfactory measures for the correction of the general social problem and to a general feeling of hopelessness in regard to the possibility of dealing satisfactorily with sexual deviations.

3. Patients of the more hopeful type, whose manifestations of sexual deviation derive either directly or indirectly from other, actually primary, personality maladjustments, of which several examples have been cited by Dr. Selling. These are the patients who during a period of stress and difficulty react to pressing conflicts and emotional stresses and frustrations by more or less temporary resort to juvenile and infantile patterns of sexual behavior as regressive phenomena. It is primarily patients of this type who need psychotherapeutic aid by qualified psychiatrists, and it is also patients of this type who respond adequately to psychotherapeutic measures. If, however, such psychotherapeutic aid is not accorded, there is a possibility that the patient will undergo still further distortion of personality which will result in continuance of his sexual deviation, thus causing an ever increasing social problem. It seems to me that at present the pressing psychiatric problem is the recognition and treatment of this type of sexual offender as a means of approaching intelligently the whole problem.

Book Reviews

Problems of Functional Correlation of the Vegetative Nervous System. A. M. Grünstein, Professor Emeritus, Editor. Contributions from the Central Psychoneurologic Institute, vol. 9. Price, 6 rubles, 50 kopecks. Kharkov, U. S. S. R.: State Medical Publications, 1937.

The aim of the collective work done in this field of research has been well formulated by Heymanovich in his conclusion that there is a definite relationship, or harmony, as he puts it, between the function of the vegetative and that of the sensorimotor nervous system. Changes occurring in one system, directly or indirectly, affect the other. Such a view may help one to understand some obscure clinical phenomena and to explain their pathogenesis. This point of view has been consistently adhered to in the twenty-two contributions which make up the present volume. The subjects discussed are of unusual interest. Itzenko, for instance, describes a syndrome resembling in many features that of Cushing, but in which the lesion was placed in the infundibulopituitary region. The outstanding sign was excessive growth of hair on the face, which resembled, especially in conditions of long standing, that of a primate, and obesity in the areas of the eighth to the twelfth thoracic metamere, combined with increased permeability of the walls of the blood vessels. In 2 cases, which have been studied pathologically, changes were observed in the sympathetic nuclei (nucleus tuberalis, nucleus supraopticus and nucleus mamillo-infundibularis).

Epstein discusses the so-called vital (sensorimotor) syndrome of Schneider and Westermann in cases of depression, in which somatic manifestations (feeling of pressure in the chest, restlessness and various paresthesias) are combined with disturbances of sleep, especially in the morning hours; Popoff describes sympathetic nervous manifestations resulting from destruction or stimulation of various cortical areas and concludes that water metabolism is regulated by the vegetative nervous system. Some forms of hemialgias, such as obscure pains in the occipital region and in the face, are considered by Heymanovich to be multiple neuralgias, i. e., neuralgia with multiple localization, caused probably by a lesion of the carotid sinus. He calls the syndrome carotid-trigeminal-temporal neuralgia. Tretiakoff emphasizes the parallelism between pressure in the spinal fluid and renal function. When secretion of the cerebrospinal fluid is reduced, secretion of urine is also decreased, and vice versa. The secretion of urine increases if the spinal fluid pressure becomes normal. Tretiakoff calls the phenomenon "liquor-urinary parallelism." It is especially noticeable when the infundibular region is affected and the regulating action of the cerebrospinal fluid pressure is inhibited.

The role of the sympathetic nervous system in epilepsy; the intervisceral or viscerovisceral reflexes (e. g., the reflex from one kidney to the other or the reflex from the rectum to the kidneys, liver or heart); the condition of the capillaries (as seen in capillaroscopic examination), and many other problems are discussed. The contributions are all based on original investigations, experimental or clinical or both. The articles are briefly summarized in English and French.

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The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

VOLUME 43 NUMBER 6

ARCHIVES OF NEUROLOGY AND PSYCHIATRY

JUNE 1940

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system and to disseminate knowledge in this department of medicine.

Manuscripts for publication and correspondence relating to the editorial management should be sent to Dr. H. Douglas Singer, Chief Editor, 30 North Michigan Avenue, Chicago, or to any other member of the Editorial Board. Books for review also should be addressed to Dr. Singer. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF NEUROLOGY AND PSYCHIATRY, American Medical Association, 535 North Dearborn Street, Chicago.

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